ARCHIVES of INTERNAL MEDICINE

VOLUME 75 FEBRUARY 1945 NUMBER 2

COPYRIGHT, 1945, BY THE AMERICAN MEDICAL ASSOCIATION

TWO CASES OF MORVAN'S SYNDROME OF UNCERTAIN CAUSE

HARRY PARKS, M.D., AND O. S. STAPLES, M.D.

ATLANTA, GA. BOSTON

About ninety years ago, Augustin Morvan, a Breton physician, was consulted by a fisherman with a septic finger. Morvan incised it and noted that his surgical manipulations caused no pain: The patient did not even wince at the contact of the bistoury. This phenomenon appeared so curious that Morvan determined to investigate the sensibility of the affected hand; to his surprise, he discovered that the hand and a part of the forearm did not feel the prick of a pin. During the next thirty years he observed 6 other similar cases of painless infections of the hand, and these he reported in 1893 in the *Gazette hebdomadaire de médecine et de chirurgie*[1] as examples of a new disease. He called this condition *parésie analgésique des extrémités superieures.*

Morvan's paper is interesting. He expressed the opinion that the source of this new disease must lie in the spinal cord, and he emphasized the dissociated sensation which his patients exhibited: "The patient can hold a burning coal in his hand without pain. Yet the feeling of touch is preserved, and the patient, his eyes blindfolded, can indicate with precision the spot where he is touched." He described the paresis and amyotrophy which were apparent in many of his patients and their various trophic disorders, such as deformed extremities, peculiar arthropathies and spontaneous fractures.

This paper stimulated great interest at once. Since its publication there has grown up a large literature on "Morvan's disease." As a rule the clinical picture of which Morvan wrote has been proved to be due to syringomyelia, with trophic lesions an outstanding feature. That leprosy may produce nearly identical symptoms has been mentioned many times; in fact, several writers have suggested that the sailors of Brittany are peculiarly liable to an atypical form of leprosy exemplified in the cases which Morvan described, and thus the leprosy of Brittany has been discussed seriously in the French literature.

A few authors have insisted that the clinical picture of Morvan's disease is not always due to syringomyelia or to leprosy and that in some cases it represents an independent disorder. Two cases of this type have been studied carefully by us in Boston, one at the Robert Dawson Evans Memorial and the other at the Children's Hospital. In both the diagnosis of syringomyelia seems improbable, the fundamental disease apparently being an unusual neuropathy of undetermined origin. These cases are reported to stimulate interest in a rare and little understood condition.

REPORT OF CASES

CASE 1.—G. A., an 8 year old American boy, entered the Robert Dawson Evans Memorial on July 22, 1936. His father and mother and one sister were living and well.

History.—The boy's delivery and his early history were normal. He had measles when he was 4 years old, chickenpox at 5 years of age and probably one-sided mumps at 7. Except for these illnesses his history was uneventful. There was no delay in walking and no mental retardation. There was no history of injury to his spine. He attended grade school and appeared to be bright and intelligent in his school work.

When the boy was 2 years old his mother noticed that he often bit and chewed his finger tips until they bled. The resultant wounds appeared to be painless and healed slowly. In those early days, also, he burned his hands several times without seeming to be aware of it. When he was 6 years old an infection developed about the nail of the right index finger. This was not painful and apparently was not accompanied by any systemic reaction. Roentgenograms of the finger showed osteomyelitis of the terminal phalanx, and this was removed. Several months before his admission to the hospital sensation in his legs seemed to become abnormal. He stumbled and fell more often than did other children of his age, and often he injured his toes, though never in such a manner as to make him complain of pain. Six months before he entered the hospital his left index finger became infected, and presently the terminal phalanx dropped off. Just before the patient came under our observation several shallow ulcerations developed on his finger tips. These healed slowly with callus-like thickening of the skin. His hands became so awkward in finer movements such as writing, buttoning his clothes and cutting food that his parents determined to send him to a hospital for treatment.

1. Morvan, A.: De la parésie analgésique à panaris des extrémités supérieures ou paréso analgésie des extrémités supérieures, Gaz. hebd. de méd. **20**:580-583, 590-594 and 624-626, 1883.

Physical Examination.—He appeared a fairly well developed but undernourished youngster, bright and intelligent. His posture was poor, with bowing of the legs and protrusion of the abdomen, but there was no obvious scoliosis. His heart, lungs and abdomen were normal. The axillary and inguinal glands were easily palpable and were firm, small, discrete and nontender. The peripheral arteries were not unusual.

The hands and feet showed a curious variety of trophic changes, which were more marked in the upper extremities than in the lower. The nails were short, thick and dark, and several were cracked and loosely attached to their matrices. The skin surrounding the nails was thickened as if it were mildly and chronically inflamed. The finger tips were rough and keratotic. There were no folds of skin over the terminal interphalangeal joints. On both thumbs and over three fingers of the right hand near their tips were small, shallow ulcers surrounded by thickened skin and extending through the subcutaneous tissues. There were many healed scars on the lower parts of both legs. The toes looked much as did the fingers but did not appear so badly damaged.

Neurologic Examination.—Examination of the nervous system revealed glovelike areas of hypesthesia or anesthesia involving both hands below the wrists and both feet and legs below the knees, with diminished reactions to pain, touch and temperature stimuli in these regions. Such hypesthesia was more marked distally than centrally, and the disturbances in the sensation of touch were more widely distributed than were the disturbances in the sensation of pain and temperature.

There was total absence of all superficial and deep tendon reflexes. No abnormal reflexes were elicited except Romberg's sign. Vibratory sensation and stereognosis seemed impaired, and it seemed probable too that the sense of muscle and joint positions was impaired. No muscular atrophy or fibrillary twitchings were observed.

The muscles and ligaments about both ankle joints were lax, permitting undue inversion and eversion of the ankle joints.

The vasomotor reactions in the hands and feet were not remarkable as judged by measurements of the temperature of the skin, which were made at the Peter Bent Brigham Hospital. There was no tremor.

Examination of the cranial nerves gave negative results except that the corneal reflexes on both sides were diminished, with slightly diminished sensitivity to pain and temperature in the face.

Laboratory Studies.—A variety of laboratory studies gave negative results. Blood counts, urinalysis, examinations of stools and chemical examinations of the blood, including determinations of phosphorus and calcium, gave normal results. Repeated Wassermann, Hinton and Kahn tests of the blood serum revealed no abnormalities. Lumbar puncture revealed a clear and colorless spinal fluid which was under normal pressure and had normal dynamics. It contained 3 cells per cubic centimeter and had a total protein concentration of 9 mg. per hundred cubic centimeters. The colloidal gold curve and the Wassermann reaction of the spinal fluid were normal.

Roentgenograms of the hands and feet showed lack of tufting of the ends of the distal phalanges but were otherwise not remarkable. Roentgenograms of the cervical, thoracic, lumbar and sacral vertebrae revealed no pathologic changes. There was no scoliosis or spina bifida.

Biopsies of skin taken from the dorsa of the wrists and from the middle finger of the right hand were not informative. No lepra cells or lepra bacilli were seen, and there were no histologic changes to suggest the presence of syphilis or of tuberculosis.

Examination of the amputated left thumb and middle finger showed thickening of the skin due to cornification of the surface epithelium and edema of the corium. No nerves or nerve filaments were seen. Microscopically there was found to be chronic inflammation of the skin

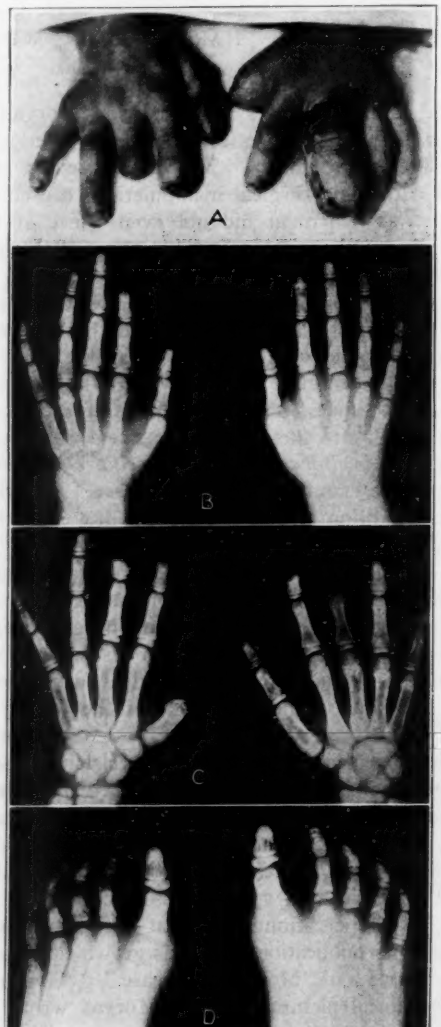

Fig. 1 (case 1).—*A*, hands, showing painless infections and their end results and abnormal nails. There is no muscular atrophy. *B*, *C*, roentgenograms of the hands, showing progressive changes in bones in the course of two years. *D*, roentgenograms of the feet, showing undeveloped phalangeal and metatarsal bones with pressure necrosis of the proximal phalanges.

and of the subcutaneous tissues with infiltration of neutrophils, eosinophils and endothelial cells. There were disappearance and degeneration of the medullated nerves, which were surrounded by a dense fibrous capsule and by lymphocytes, plasma cells and endothelial cells. The

phalanges showed marked atrophy and decalcification without periosteal reaction or osteomyelitis. An occasional arteriole was almost completely occluded by fibrosis and lymphocytic infiltration.

In 1943 biopsy of the small nerve of the right foot was performed at another hospital. This was reported to show no inflammatory changes.

Course.—Up to the time of writing the patient's subsequent history has consisted of repeated painless infections of the fingers and hands following minor trauma. At one time he bit off a small portion of the tip of his right middle finger. An infection followed, with much edema and necrosis of the soft tissues, until finally the terminal phalanx of this finger was found lying loose in the tissues and was removed. This episode was followed by a palmar abscess, which was drained without anesthesia. It was only on very deep probing that there was any complaint of pain. On another occasion an infection of the left thumb and of the right middle finger developed. The thumb required amputation at the metacarpophalangeal joint and the finger at the proximo-interphalangeal joint. Cultures from these wounds contained hemolytic streptococci and Staphylococcus aureus. Six months after the first examination his condition was about as it had been except that only greatly diminished biceps reflexes were obtainable for a time. The spinal fluid was reexamined and was entirely normal.

On the hypothesis that the child might have syringomyelia and that radiation might be of some therapeutic help, he was given a course of roentgen treatment of the spinal cord. The benefit obtained from this was by no means striking or certain.

A report seven years after the patient was first seen revealed that his general health was good. Recurrent ulcerations of the finger tips and further loss of three additional phalanges had occurred; also he has had trouble with both feet.

CASE 2.—J. P., a 12 year old American girl, entered the Children's Hospital on July 27, 1938. It may be of some interest that her parents were first cousins. She had three brothers and one sister, who were living and well. One sister had died in infancy of some undetermined cause.

History.—The patient had had measles, mumps, whooping cough and scarlet fever in infancy. Her social background was notably poor, so that her diet had often been inadequate for varying lengths of time.

Three and a half years before entering the hospital she began to have weakness in her legs and recurrent painless ulcerations and infections in her fingers and toes.

Physical Examination.—She was fairly well developed and well nourished and appeared normally intelligent. Her posture was good, and there was no demonstrable scoliosis. Examination of the heart, lungs and abdomen revealed no abnormalities.

The skin about the nails of both hands was thickened, reddened and cracked, and the nails were short and irregular. Her feet showed symmetric equinovarus deformities, which could not be corrected by passive motion. There were large calluses over the lateral plantar aspects of both feet, with numerous fissures in the skin of this region. On the right foot there was an ulcer, which appeared to be chronically infected.

Neurologic Examination.—Neurologic examination revealed symmetric glovelike areas of anesthesia or of diminished sensitivity to pain, temperature and touch, involving all four extremities and most marked distally. The disturbances in the sensation of touch were more widely distributed than the disturbances in the sensations of pain and temperature. Bone conduction seemed normal, although sense of position was lacking in the fingers and toes. The deep tendon reflexes were diminished, and no abnormal reflexes were obtained. The cranial nerves seemed normal.

There was symmetric weakness of the anterior tibioperoneal muscles, of the extensors of the toes, of the short and long toe flexor muscles of both feet and of the palmar interosseous muscles of both hands. There was no obvious muscular atrophy, however, and no twitching or tremor. There was no evident vasomotor abnormality.

Laboratory Studies.—Just as in the other case, all laboratory studies gave negative results. The spinal fluid was normal. Roentgenograms of the spine, the chest, the arms and the legs were normal except for the absence of "tufting" of the ends of the terminal phalanx of the right great toe and of the left middle finger. There was no scoliosis or spina bifida.

Fig. 2 (case 2).—Hands and feet, showing abnormal nails. There is no muscular atrophy.

Specimens of skin taken from the left forearm and from the right foot in the region of the ulcer revealed nothing remarkable on histologic examination. Stains for tubercle and lepra bacilli revealed no organisms, and tuberculosis did not develop when material from these tissues was inoculated into a guinea pig. Biopsy of a section of the saphenous nerve just above the ankle gave negative results.

Course.—A report from this patient three years later indicated that there had been no appreciable change in her condition. Striking changes in the bones of the feet, apparently of a trophic nature, had developed.

These 2 cases, clearly, have several common features. In each there was a symmetric peripheral type of hypesthesia involving all four extremities, more marked distally than centrally, and accompanied by peculiar trophic changes.

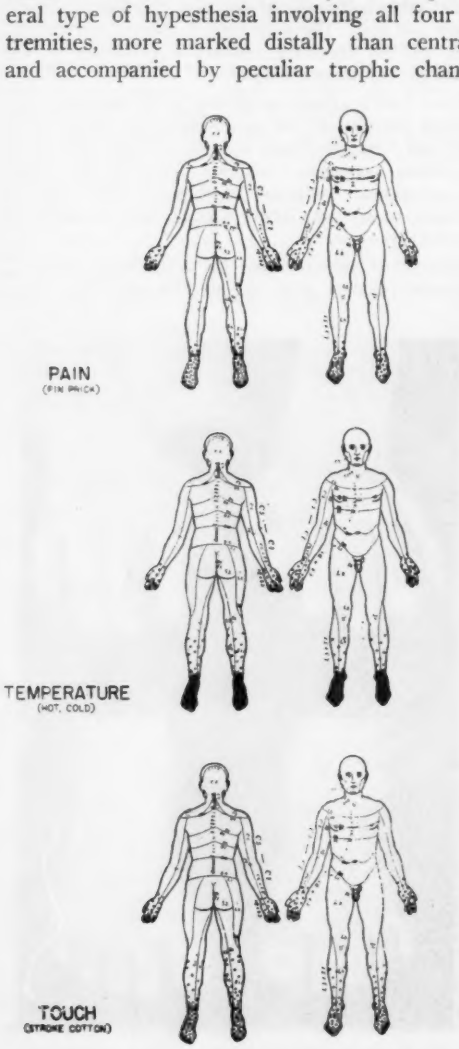

Fig. 3 (case 2).—Chart showing the distribution of anesthesia and hypesthesia. Black indicates areas of anesthesia, dots areas of hypesthesia. The findings in case 1 were essentially identical.

Neurologic examination gave negative results in other respects except that all deep reflexes were either diminished or absent. Roentgenograms revealed as an early lesion loss of tufting of the terminal phalanges in the hands and feet. There was a varying degree of muscular weakness without apparent muscular atrophy. Biopsies of the skin were not informative, and in 1 case examination of a peripheral nerve gave no remarkable results. Attempts to prove the presence of tuberculosis or of leprosy yielded negative results.

SIMILAR CASES IN THE LITERATURE

We have reviewed all the reports of "Morvan's disease" occurring in children. We believe that 7 cases resembling ours have been described and that they do not present the clinical picture ordinarily associated with syringomyelia. A summary of these cases follows:

Head [2] has described the case of a 4 year old girl whom he saw because of frequent falls and painless injuries of the hands and feet. When she was 8 months old she had an infection of the right index finger, which was slow in healing; later she had successive infections of all her fingers, at one time losing a thumb spontaneously as a result of a simple paronychia. When Head saw her all of the terminal phalanges were lost; there was no sensation of pain or of temperature in the arms or the legs, and the deep tendon reflexes were absent. There was no muscular atrophy, but the patient's gait was unsteady. The cranial nerves seemed normal.

Bousquet [3] reported a case of a 9 year old girl who when she was 3 years old had a painless burn on the finger, resulting in an infection which healed slowly. When she was 4 years old she began to bite her finger nails to the point of bleeding, without experiencing any pain. When she was 6 years old she had a painless wound of the left heel, which required frequent incisions for drainage. There were trophic changes in both hands, since all the nails had disappeared. Sensory examination revealed absence of the sensations of pain and temperature below both knees and both elbows, although tactile sensation was intact. In this case the reflexes of the tendons and the skin were normal.

Bonnett and Goyet,[4] Bonnett [4a] and Delore, and Barbier and Jarricot [4b] reported a case which was followed for twenty-three years. When first observed the patient had sensory and trophic disturbances of the hands and feet. There was symmetric loss of the sensations of pain and temperature in the hands, with preservation of tactile sense, but all forms of sensation were lost in the feet. The deep reflexes were absent

2. Head, H.: Morvan's Disease: Case Report, London Hosp. Gaz. **10**:5-7, 1903.

3. Bousquet: Un cas de syringomyélie chez l'enfant, Ann. de méd. et chir. inf. **10**:673-679, 1906.

4. Bonnett, L. M., and Goyet: Syringomyélie à forme de maladie de Morvan chez un enfant, Lyon méd. **113**: 1017-1020, 1909.

4a. Bonnett, L. M.: Syringomyélie a forme de maladie de Morvan traité par la radiothérapie bon resultat, Lyon méd. **130**:1051-1054, 1921.

4b. Barbier, M., and Jarricot, H.: Sur un de "syringomyélie a forme de Morvan," Lyon méd. **148**: 374-377, 1931.

in the legs, although they were present in the arms. He was given several courses of roentgen therapy without any noticeable effect. Several years later, when he was 20 years old, he improved for a period of three years although roentgenograms of the phalanges showed characteristic resorption of bone. Later there was exacerbation of the process with recurrence of trophic changes in the feet. When he was 36 years old the disturbances in sensation were unchanged. Both knee jerks were absent, although the left ankle jerk was obtainable. There was no muscular atrophy, and his general health was good. This case has been followed over a longer period than any other case recorded. The striking feature of it is the small apparent progress of the disease during more than twenty years.

Cruchet, Petges and Joulia [5] have studied a 7 year old boy who at the age of 3 began to have "indolent blisters" on his arms and legs; these were followed by painless ulcers and subsequent loss of several phalanges. The fingers and toes were short and thick. The movements of the hands were awkward. On the palmar surfaces of the feet were perforated ulcers, which at times had drained bony fragments, so that some of the toes were reduced to conical stumps. The deep reflexes were absent. There was loss of all forms of sensation below the knees and wrists, with diminution of sensation from the knees to the hips and thighs and from the wrists

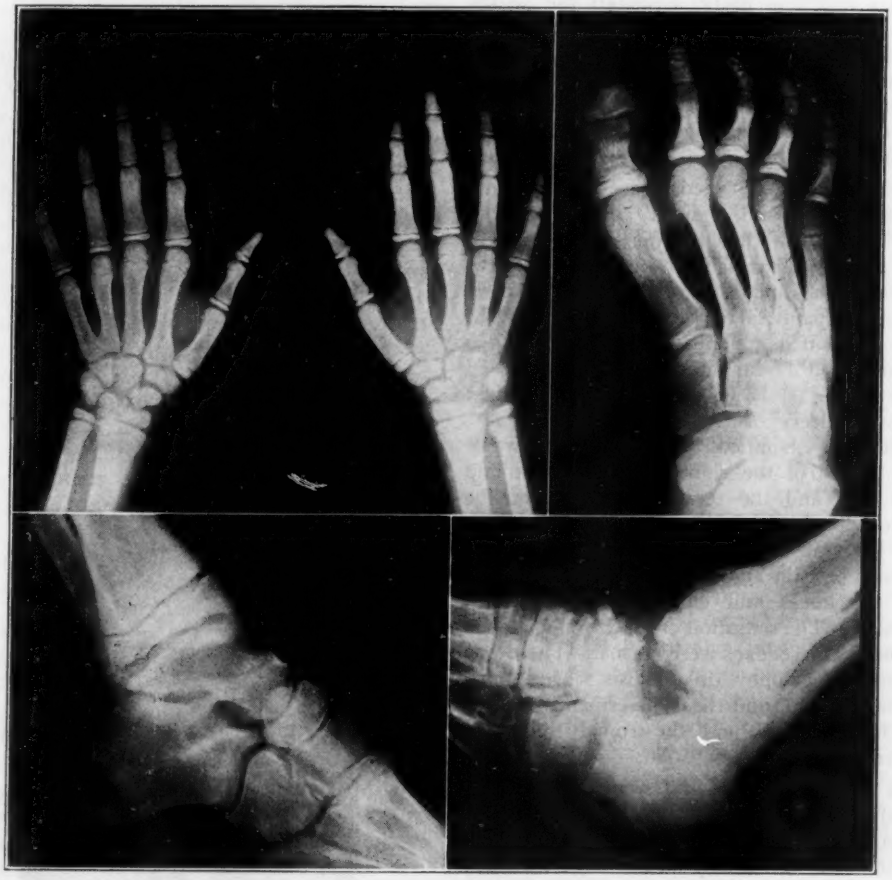

Fig. 4 (case 2).—Roentgenograms of the hands and a foot. The early lesion appears to be loss of tufting of the terminal phalanx, shown in the left middle finger and great toe. The roentgenograms of the foot show progressive changes in bone in eighteen months. There have developed condensation and destruction of the talus and to a lesser extent of the os calcis and of the navicular. There is moderate osseous debris in the region of condensation. The worse involved foot appeared normal when the patient was first seen.

5. Cruchet, R.; Petges, G., and Joulia: Un cas de maladie de Morvan chez un enfant de sept ans, Bull. et mém. Soc. de méd. et chir. de Bordeaux, 1920, pp. 282-290.

to the forearm. Lepra bacilli were not found in the discharge from the ulceration or in the nasal discharge. The Wassermann reactions of the blood and the spinal fluid were negative.

Wagner [6] reported the case of a 15 year old girl who began to have painless blisters and ulcers of the toes when she was 9 years old. The terminal phalanges of the large toes were absent, and ulcerations were present on their palmar surfaces near the bases. There was no muscular atrophy. The hands had a diminished sensation of temperature, although the senses of pain and touch were normal, and in the feet the sensations of both temperature and pain were less acute than the normal though not entirely absent. Roentgenograms of the feet showed destruction of the phalanges and of the metatarsal bones.

Gaté and Riou [7] reported 2 cases, the patients being a brother and a sister. The man who was 27 years old when he was first examined, gave a history of having been unable to feel heat for many years and as a result having experienced many painless burns. When he was 13 years old he had a nonpainful swelling in the right knee and a year later a similar process in the left knee. At 17 he had a series of painless perforated ulcers of the feet, so that finally, when he was examined, both index fingers, the middle finger of the right hand, the first and second toes and the terminal phalanx of the third toe of the right foot were absent. There was a perforated ulcer of the right heel. The sensations of pain and temperature were absent below the knees and elbows and diminished proximally. The sensation of touch was but little impaired. The reflexes were normal. There was no muscular atrophy or scoliosis. The spinal fluid was normal, and the Wassermann reaction of both the blood and the spinal fluid was negative.

This man's sister was first seen when she was 38 years old. Her difficulties began when she was about 13 and appear to have been much like her brother's. Eventually all her fingers became affected; she lost one foot and had only two toes on the other. In this patient there were no abnormal reflex changes and there was no muscular atrophy.

COMMENT

Each of these 7 cases reported by foreign authors appears to us much like the 2 studied in Boston. Whatever the disease may be, it appears to develop in young people of either sex. The first symptoms are sensory and usually consist of absence of pain with burns or other injuries. Later there develops loss of the sensation of pain, temperature and usually touch in the distal parts of all four extremities. Trophic changes soon become prominent in the form of ulcers, atrophy of the bones and changes in the nails; spontaneous amputation of small parts becomes necessary by reason of infection. On physical examination the superficial and deep tendon reflexes may be absent, diminished or normal. No paralysis, muscular weakness or atrophy develops, and evidence of involvement of the upper motor neurons or of the lateral or the pyramidal tract is strikingly absent. The course of the disease appears to be relatively

Fig. 5.—The late result of Morvan's syndrome in a patient known to have had the disease for fourteen years. The patient was seen by Dr. Cruchet, who has permitted us to use the illustration.

6. Wagner, I.: Beitrag zur familiären lumbosacralen Syringomyelie, Monatschr. f. Kinderh. **53**: 137-152, 1932.

7. Gaté, J., and Riou, J.: Troubles trophiques et troubles de la sensibilité réalisant un syndrome de Morvan familiel, Lyon méd. **157**:102-106, 1936.

benign. Unfortunately observations at necropsy have not been described.

Questionnaires were sent to several authors who reported the cases described, asking for follow-up notes and particularly for results of necropsy. These letters elicited no significant information. The 1 case which was followed for more than twenty years, however, and the history of our own cases suggest that any rapid progressiveness is unlikely.

The authors whose cases have been mentioned discussed them as problems in differential diagnosis, hypertrophic neuritis, leprosy, Raynaud's disease and syringomyelia. The preferred diagnosis in each instance was syringomyelia.

Compared with cases of syringomyelia as usually reported, these cases seem somewhat atypical. In syringomyelia there frequently is a segmental distribution of dissociated sensation, that is, preservation of the sense of touch with loss of the sense of pain and temperature in a given area. In this group of cases there was impairment of all forms of sensation, occurring symmetrically in all four extremities. In syringomyelia there are likely to develop signs of involvement of the lateral column, such as exaggerated reflexes or spasticity, signs of involvement of the anterior horn, such as loss of reflexes, atrophy or fibrillations, and signs of involvement of the posterior horn, such as loss of the sense of position and loss of vibratory sensations. These changes appear either singly or in combination in the majority of cases of syringomyelia. Such manifestations, on the whole, were strikingly absent in our cases. The distribution of the neurologic signs of syringomyelia is usually asymmetric. In these cases the symmetry of the involvement was striking. Syringomyelia follows a course which is chronic and slowly progressive but often more rapid than that in the cases reported here seems to have been. While trophic changes such as those in our cases have been observed frequently in typical cases of syringomyelia, such trophic phenomena are an additional element in the picture of syringomyelia and do not dominate the clinical picture as much as in the cases described here.

In our 2 cases biopsies were of little assistance. The exact diagnosis remains obscure. If our patients have some form of peripheral neuritis, it is an unusual form unless one assumes that the sensory rather than the motor fibers are predominantly affected. On the other hand, if they have a form of syringomyelia, it is also an unusual form of this disease and unlike that in most of the cases reported.

A few years ago Dr. René Cruchet, then professor of medicine at the University of Bordeaux, spoke in Boston on Morvan's disease and allowed us to study his manuscript. He saw our patient, G. A., and suggested an interesting possibility. He did not think this boy had syringomyelia, though he agreed that he had a form of Morvan's disease, or, as he preferred to call it, Morvan's syndrome. He wondered whether the young man's condition could have arisen from a lesion located in the so-called trophic center of the medulla, an area which was mapped out by Laruelle [8] to include the nucleus of the lateral cornua and the superior sympathetic nucleus of Jacobson. Cruchet expressed the opinion that this area exists. He hypothesized that an inflammatory or degenerative lesion or even a congenital imperfection sharply localized to this area might result in extraordinary trophic disturbances; by postulating a lesion in that region he explained in a more or less plausible manner the development of the picture of Morvan's syndrome in persons without apparent syringomyelia or leprosy.

How seriously such an apparently fanciful suggestion should be taken is uncertain. Seemingly, however, there is a peculiar neurotrophic disorder of unknown cause occurring in children which runs a chronic course. It is characterized by symmetric loss of sensation in the arms and legs and by notable trophic changes. It may resemble certain forms of syringomyelia but lacks the characteristic segmental distribution of sensory symptoms with dissociated sensation which is ordinarily found in this disease. It lacks also amyotrophy, spasticity and other signs indicating involvement of the upper or lower motor neurons or of the spinal tract. It is not leprosy. It is a rare disease, which warrants further study.

915 Chandler Building.
262 Beacon Street.

8. Laruelle, L.: La structure de la moelle epinière en coupes longitudinales, Rev. neurol. **67**:695-725, 1937.

PNEUMOCOCCIC ENDOCARDITIS

C. M. TINSLEY, M.D.
SAN FRANCISCO

Graves [1] in 1843 offered what was probably the first description of this disease. He reported the observations at autopsy in a case of pneumonia and described endocarditis of a bicuspid pulmonary valve.

The great increases in information concerning bacterial endocarditis which were made in the latter half of the nineteenth century were ushered in by Ormerod's Goulstonian Lecture of 1851.[1] Here, for the first time, a clear distinction was drawn between ulcerative and rheumatic endocarditis. The basis of the clinical recognition of bacterial endocarditis was established firmly by Kirkes in 1852.[2] He described embolic phenomena in various forms, occlusion of the arteries of the leg, hemiplegias and cutaneous petechiae and argued that these were due to mechanical obstruction of the vessels by pieces detached from the "large fibrinous masses on the heart valves." Stokes [1] in 1854 defined endocarditis and stated that "there is no pathognomonic sign of its existence, and its diagnosis depends on the recent production of a valvular murmur or the existence of special morbid states of the system, which predispose to inflammation of the heart." Wilks in 1868 [3] reemphasized Kirkes' studies and also pointed out that valvular endocarditis may act as "a wound at the center of the circulation" and so by dissemination of purulent infarcts give the symptoms of "pyemia."

The ensuing years mark the great growth of the science of bacteriology, and in 1875 Klebs first described the pneumococcus. In 1881 Pasteur and Sternberg, working independently, isolated pneumococci for the first time through animal passage. In April 1884 Fraenkel [4] made the first report of his studies, which were to fulfil later (1886) all of Koch's postulates. He demonstrated the diplococci in lesions of endocarditis, pleuritis, pericarditis and nephritis and correctly assumed that metastases might arise from a pulmonary lesion.

During this time clinical studies had been keeping abreast of increasing bacteriologic knowledge. Osler in 1881 [5] spoke of finding "micrococcus balls" in 4 cases of endocarditis complicating pneumonia. He was not ready to assert that the "micrococcus balls" were the cause of the disease, but called attention to the frequency with which this condition and meningitis accompany pneumonia. One year later Bozzolo [4] concluded from clinical observations that pleurisy, pericarditis, endocarditis and meningitis were frequently associated with lobar pneumonia and that this association was due to a single infective agent. Netter [1] in 1886 published a comprehensive review of ulcerative endocarditis as a complication of pneumonia. He demonstrated pneumococci in the vegetations and in the blood stream and produced the disease experimentally.

INCIDENCE

Pneumococcic endocarditis is generally considered a relatively rare disease, almost a medical curiosity, although medical literature contains numerous reports of individual cases. In 1885 Osler [6] reported 16 instances identified in 103 necropsies on patients who had died of lobar pneumonia. In one of the classic papers on the subject of infectious endocarditis Thayer [7] described 38 cases of pneumococcic endocarditis of his own and an additional 41 cases collected from the literature. These represented respectively 12.4 per cent and 14.7 per cent of 306 personal cases and 538 collected cases of all kinds of bacterial endocarditis. Perry [1] in his monograph "Bacterial Endocarditis" collected 1,000 cases in which the causative bacterial agents were

From the Department of Medicine, Stanford University School of Medicine, and the San Francisco Hospital, Department of Public Health.

1. Perry, C. B.: Bacterial Endocarditis, Bristol, John Wright & Sons, Ltd., 1936, p. 137.

2. Willius, F. A., and Keys, T. E.: Cardiac Classics, St. Louis, C. V. Mosby Company, 1941, p. 473.

3. Willius and Keys,[2] p. 577.

4. White, B.: The Biology of Pneumococcus, New York, The Commonwealth Fund, 1938, p. 799.

5. Gordon, A.: Acute Endocarditis, Canad. M. A. J. **42**:182 (Feb.) 1940.

6. Osler, W.: Malignant Endocarditis, Lancet **1**:416, 459 and 505, 1885.

7. Thayer, W. S.: Bacterial or Infective Endocarditis, Edinburgh M. J. **38**:237 (April); 307 (May) 1931.

well established. In 112 (11.2 per cent) the disease was due to the pneumococcus. Goldburgh, Baer and Lieber [7a] found that in 62 of 646 cases (9.6 per cent) of acute bacterial endocarditis observed in 26,007 autopsies done over a twenty year period the pneumococcus was the infecting organism. Table 1 shows the incidence of pneumococcic endocarditis among pneumococcic infections in general [7b] and among pneumococcic infections in patients on whom autopsies were performed.[7c]

MATERIALS FOR THE PRESENT STUDY

The present is a statistical and clinical study of 16 patients with pneumococcic endocarditis. Autopsies were performed on 13 of these patients, constituting 0.25 per cent of 5,503 consecutive autopsies (1933-1944). There were 118 cases of lobar pneumonia (2.1 per cent of all cases in which necropsies were performed). There were 36 cases (0.65 per cent of all the cases in which necropsies were performed) of acute bacterial endocarditis for which the cause was considered definitely established by clinical examinations and necropsy. In these, 13 infections were due to the staphylococcus, 2 to the gonococcus, 8 to hemolytic streptococci and 13 to the pneumococcus (36 per cent).

Data from the cases of 3 additional patients will also be used. Permission for autopsies on 2 of these patients could not be obtained. The third patient is living and is receiving penicillin therapy.

PATHOLOGY

The vegetations in pneumococcic endocarditis vary greatly in size, color and distribution. Thayer [7] stated that "the process is, almost invariably, an acute ulcerative endocarditis especially notable for early and extensive destruction of tissue resulting in erosions of valves with aneurysms, rupture or burrowing ulcers." Ruegsegger [8] agreed closely with this conclusion. The vegetations vary in size from a mere excrescence to a huge growth that fills a ventricle almost completely. The masses are usually soft, friable and grayish red. The pneumococcus may attack the endocardium, leaving the valves intact.

Table 2 shows the site of the pneumococcic valvulitis as given in series of autopsies presented by various authors. The well known predilection of the pneumococcus for the valves of the left side of the heart is illustrated. However, Goldburgh, Baer and Lieber [5] and Allen [9] felt that this organism produces a relatively greater number of right-sided lesions than do other organisms causing acute bacterial endocarditis. The former authors found vegetations restricted to the tricuspid valve in only 1.9 per cent of 584 cases of acute bacterial endocarditis due to infec-

TABLE 1.—*Incidence of Pneumococcic Endocarditis Among Pneumococcic Infections in General and Among Pneumococcic Infections of Patients Subjected to Autopsy*

Author	Number of Cases of Pneumococcic Infections	Number of Cases of Pneumococcic Endocarditis	Percentage of Pneumococcic Endocarditis	Number of Cases of Pneumococcic Infections Identified at Autopsy	Number of Cases of Pneumococcic Endocarditis	Percentage of Cases of Pneumococcic Endocarditis Identified at Autopsy
Rosenblüth (1932)..	150	5	3.3	...	..	....
Ruegsegger (1938)..	655	19	2.9	....	..	....
Moore (1940).....	1,469	54	3.6	...	..	....
Osler (1885).....	...	..	...	108 (lobar pneumonia)	16	15.5
Lord (1932).....	...	..	...	337 (lobar pneumonia)	14	4.15
Finland (1937).....	...	..	...	684	31	4.5
Goldburgh (1942)...	...	..	...	1,041 (lobar pneumonia)	62	5.9
Tinsley (1944).....	...	..	...	118 (lobar pneumonia)	13	11.0

7a. Goldburgh, H.; Baer, S., and Lieber, M.: Acute Bacterial Endocarditis of the Tricuspid Valve, Am. J. M. Sc. **204**:319 (Sept.) 1942.

7b. Moore, F. J.; Thomas, R. E.; Kistler, M.; Ireland, R. M., and Hallstone, V. E.: Pneumococcic Pneumonia, Arch. Int. Med. **66**:1290 (Dec.) 1940. Rosenblüth, M. B.: Pneumococcus Endocarditis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 3, p. 983.

7c. Finland, M.; Brown, J. W., and Ruegsegger, J. M.: Anatomic and Bacteriologic Findings in Infections with Specific Types of Pneumococci, Including Types I to XXXII, Arch. Path. **23**:801 (June) 1937.

8. Ruegsegger, J. M.: Pneumococcic Endocarditis, Arch. Int. Med. **62**:387 (Sept.) 1938.

9. Allen, A.: A Case of Bacterial Endocarditis Illustrating the Mechanism of Localization and Nature of the Vegetations, Am. Heart J. **21**:667 (May) 1941; Mechanism of Localization of the Vegetations of Bacterial Endocarditis, Arch. Path. **27**:399 (March) 1939; Nature of the Vegetations of Bacterial Endocarditis, ibid. **27**:661 (April) 1939.

tive agents other than the pneumococcus, while in 14 per cent of the cases of pneumococcic endocarditis there were vegetations of this type.

In 77 per cent of the patients in the present series pneumococcic masses were confined to the aortic and the mitral valve; these patients constituted 54 and 23 per cent respectively of the total number. Involvement of the tricuspid valve alone was seen in only 1 patient, 7 per cent of the total number. The remaining 2 patients showed lesions of both the aortic and the tricuspid valve. In 6 of the 7 patients in whom there was involvement of only the aortic valve perforation of a cusp occurred. This also took place in 1 of the 3 patients who had vegetations only on the mitral valve. An aortic cusp was eroded in each of the patients in whom there were lesions of both the aortic and the tricuspid valves.

2 patients on whom autopsies were not done or in the third patient, now receiving treatment. Thus it is seen that the incidence of previous valvular damage given by Thayer (37.5 per cent) and that demonstrated by the present series (46 per cent) agree moderately well and are in sharp contrast to the incidence reported by Ruegsegger (6.6 per cent).

The data available are all based on series that are fairly small and are therefore influenced greatly by individual cases. It is apparent also that the majority of the cases of pneumococcic endocarditis occur on valves undamaged previously. Perhaps, however, the high proportion of instances in which the valves were damaged should be more strongly emphasized and the clinician should be especially concerned with the possibility of the development of pneumococ-

TABLE 2.—*Site of Acute Pneumococcic Endocarditis*

Site of Cardiac Lesion	Thayer		Goldburgh		Ruegsegger		Lord		Tinsley		Combined	
	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%	Cases	%
Left side	30	81	46	74	13	86	18	78	10	77	117	78
Right side	3	8	9	15	1	7	3	13	1	7	17	11
Both sides	4	11	7	11	1	7	2	9	2	16	16	11
Total no. of cases	37		62		15		23		13		150	

Acute Valvulitis	Goldburgh		Ruegsegger		Tinsley		Combined	
	Cases	%	Cases	%	Cases	%	Cases	%
Aortic	18	29	7	46	7	54	32	36
Mitral	23	37	4	27	3	23	30	33
Tricuspid	9	14	1	7	1	7	11	12
Aortic and mitral	5	8	2	13	..	..	7	8
Aortic and tricuspid	3	5	1	7	2	16	6	7
Mitral, aortic, tricuspid	1	2	..	..	..	..	1	1
Mitral, tricuspid, pulmonic	1	2	..	..	..	..	1	1
Mitral, aortic, tricuspid, pulmonic	2	3	..	..	..	..	2	2
Total number of cases	62		15		13		90	

Preexisting valvular disease is believed to have little effect on whether acute valvulitis is to occur. Thayer [7] found that in 37.5 per cent of 38 cases there was evidence of previous valvular damage. Ruegsegger [8] found that antecedent valvular disease existed in but 1 of 15 cases, reported by him, of pneumococcic endocarditis in which autopsies were performed. Davis and Weiss [10] reported that in only 7 of 5,215 cases in which autopsies were performed was there acute endocarditis secondary to a pneumonic process, the entire complex occurring, apparently, on previously normal valves. However, in the present series 6 of 13 patients on whom autopsies were performed showed either clinical or histologic evidence of preexisting valvular disease. There was no evidence of antecedent valvular disease in the cic endocarditis in a patient who has had valvular disease or who has a convincing history of a disease that produces damaged valves.

It is beyond the scope of this paper to give an extended discussion of the experimental production or the method of localization of bacterial endocarditis. However, the condition can be produced experimentally on previously undamaged valves by repeated injections of bacteria. Wright,[11] using streptococci and pneumococci, found that infection of the valves of the hearts of rabbits is most likely to occur in animals so treated with vaccines that demonstrable antibodies are present in the blood stream at the time of injection. Wadsworth [12] has described similar

10. Davis, D., and Weiss, S.: The Relation of Subacute and Acute Bacterial Endocarditis to Rheumatic Endocarditis, New England J. Med. **208**:619 (March 23) 1933.

11. Wright, H. D.: Production of Experimental Endocarditis with Pneumococci and Streptococci in Immunized Animals, J. Path. & Bact. **29**:5 (Jan.) 1926.

12. Wadsworth, A. B.: A Study of the Endocardial Lesions Developing During Pneumococcus Infections in Horses, J. M. Research **39**:279 (Jan.) 1919.

findings—the development of bacterial endocarditis in horses being immunized against the pneumococcus. Keefer [13] stated that it seems significant that the valves became infected only after the antibody titer became high, the antibodies aiding in the clumping and localization of the bacteria. He further stated that the equine endocarditis demonstrated by Wadsworth "corresponds closely to cases of endocarditis in man in which lesions develop on previously normal heart valves, for most of the patients have had bacteremia and have developed antibodies."

As for the selective localization on the valves of the left side of the heart, Ruegsegger [8] suggested that this is no more than should be expected, since in most cases the lungs are the portal of entry. A theory which has long been held is that the higher pressure in the left lung in some way contributes to lower resistance in the tissue. A possible explanation for the increased incidence of valvular lesions of the right side of the heart in pneumococcic endocarditis is that offered by Allen.[9] He expressed the view that all vegetations are produced and localized as the result of "impact, pressure, and contact" of the blood stream and the valves of the heart and that previous damage to valves serves to augment these forces. However, as the virulence of the infecting organism increases, "the necessity for pressure, impact, and contact diminishes," and it is less necessary that there be a previously damaged valve for the bacteria to lodge on. It is to this increased virulence of the infecting organism that he attributed the increased incidence of valvular involvement of the right side by such organisms as the pneumococcus.

CLINICAL FEATURES

The range of ages in the 16 patients was from 27 to 84 years, the average being 50 years. Eleven of the patients were above 45 years of age. The observation that acute pneumococcic endocarditis is a disease primarily of the fourth, fifth, sixth and seventh decades has been a remarkably constant feature of all studies on this subject. This is in contrast to the well known fact that subacute bacterial endocarditis is primarily a disease of younger persons. Twelve of the patients were men, and 4 were women. That they were all white is presumably due to the low proportion of other races in our service.

Lord [14] stated that in about one third of the cases of pneumococcic endocarditis the portal of entry is not definite. Thayer [7] found that in 83.3 per cent of his 38 cases the disease followed pneumonia. In 79 per cent of the cases reported by Ruegsegger [8] acute bacterial valvulitis followed lobar pneumonia. In the present study it was found that in 12 patients (75 per cent) pneumococcic endocarditis followed lobar pneumonia and that in 2 there was associated pneumococcic meningitis. In 1 patient the condition started with acute otitis media and mastoiditis. In the remaining 3 patients (19 per cent), including 1 having pneumococcic meningitis, no obvious portal of entry could be found.

Clinical evidence of cardiac disease was suggested by modest cardiac enlargement in 4 patients. One patient, 84 years of age, was known to have myocardial disease, for electrocardiograms taken ten years previously had shown a defect in intraventricular conduction. Repeat tracings during his final illness showed no changes. Two patients were reported to have a loud, musical systolic murmur, heard over the entire precordium. In only 1 patient is irregularity of rhythm reported to have developed during the course of the disease. In this instance auricular fibrillation was diagnosed clinically, digitalis was given and the rhythm reverted to a sinus mechanism within twenty-four hours. In this patient there was associated acute purulent pericarditis and myocarditis.

At necropsy, however, the weights of 7 hearts were found to be 400, 420, 460, 500, 520, 520 and 660 Gm. respectively. No explanation could be found for the hypertrophy in 1 patient, a 28 year old man. The enlargement in 5 cases was considered to be due either to mild valvular disease or to arteriosclerotic heart disease. In the remaining patient, a 27 year old man, autopsy revealed endocarditis of the mitral valve with fenestration of a cusp, great hypertrophy and dilatation of the left auricle, and embolism of the left descending coronary artery with myocardial infarction.

Purpura was present during the course of the illness in only 5 patients. The spleen was palpable in but 2 patients. Yet at autopsy the spleen was considerably enlarged, those of 5 patients weighing from 330 to 430 Gm. each. Clubbing of the fingers was noted only once, and this was in the patient with the longest clinical course, probably seventy to seventy-five days.

A remarkably constant feature was the presence or the development of hypochromic anemia. It was not unusual for the patient's hemoglobin to decrease by 25 per cent and reach a level that demanded repeated transfusions. The number of

13. Keefer, C. S.: Pathogenesis of Bacterial Endocarditis, Am. Heart J. **19**:352 (March) 1940.

14. Lord, F. T.: Pneumococcus Endocarditis, New England J. Med. **207**:767 (Nov. 3) 1932.

leukocytes was below 10,000 in but 2 instances, 1 of which was a terminal manifestation of the overwhelming infection. One patient repeatedly showed over 40,000 leukocytes, the highest total being 46,800. The vast majority of the counts were between 20,000 and 25,000. There was invariably an increase in the number of polymorphonuclear leukocytes and nearly always an increase in the number of banded forms.

Three of the 16 patients showed numbers of red cells in the urinary sediment. Red blood cell casts were not demonstrated. In 2 patients acute embolic focal nephritis was demonstrated at autopsy. In 1 of these cases the blood urea was 41 mg. per hundred cubic centimeters of blood, and in the other it was 91 mg. per hundred cubic centimeters at the patient's entry into the hospital and rose terminally to 126 mg. The microscopic hematuria present in the third patient may have been the result of the therapy with sulfonamide compounds. In a fourth instance the blood urea was 135 mg. per hundred cubic centimeters, but subacute glomerulonephritis was found that seemed surely to antedate the terminal illness.

In all but 1 case cultures of the blood showed the growth of pneumococci. In the majority of instances other studies on the sputum, the empyema fluid, the cerebrospinal fluid and the pericardial fluid were also done. In every case the same organism was identified from all mediums. The following types of pneumococci were found by culture of the blood: group IV, five times; type XII, three times; type XXV, two times, and types I, VII, X, XVIII and XX each once. In 1 case the organism was cultured from the valves of the heart at necropsy; morphologically and culturally it was a pneumococcus which did not show capsular swelling with the serums of types I, II or III.

The signs of acute pneumococcic endocarditis usually appear shortly after the onset of the pneumococcic infection. However, they may follow by days or even weeks what has appeared to be an uncomplicated recovery from such an infection. If the valvulitis merges with the acute pulmonary, meningeal or mastoid infection, the diagnosis is very likely to be overlooked. The onset is usually abrupt and ushered in with a sudden rise in temperature and possibly a chill. It may follow an afebrile period. It may happen during defervescence from pneumonia. From this point on the temperature is nearly always continuously elevated. Paroxysms of shaking chills and fever are not uncommon. There are usually a marked aggravation of the patient's symptoms and the signs of profound toxemia.

The course is usually a rapidly fatal one. Thayer [7] found that 88 per cent of patients live less than four weeks and 92.5 per cent less than two months. The patients in the present series were hospitalized on account of their fatal illness over periods as short as two days and as long as fifty-one days. As nearly as could be determined, the length of their present illness varied from seven to approximately seventy days. It is not implied that acute endocarditis was in existence for the longest periods, for it is impossible to be sure of the exact point at which valvulitis began. Most deaths from this disease are due either to great toxemia or to meningitis. Thayer [7] found that 55 per cent of his patients had terminal meningitis, and he expressed the opinion that this is one of the distinctive features of this disease. Ruegsegger [8] found that 68 per cent of the patients in his series died of meningitis. In the present study 5 of 15 patients died with meningitis. Two deaths were in part due to cardiac insufficiency, and in both patients aortic insufficiency had developed as a result of the ulceration of one or more valve cusps by the infectious process.

DIAGNOSIS

The signs and symptoms necessary for the diagnosis of acute pneumococcic endocarditis are in most respects no different from those needed to establish the diagnosis of subacute bacterial endocarditis. However, it must be remembered that such signs as splenomegaly, purpura and infarction of various organs do occur in a probably significantly smaller number of cases of pneumococcic endocarditis than of subacute bacterial endocarditis. Furthermore, evidence of preexisting valvular disease is present in only a fairly small percentage of the cases of pneumococcic valvulitis. One of the most necessary features for the confirmation of the diagnosis is to obtain growth of the pneumococcus in a blood culture. Prolonged pneumococcemia is in itself presumptive evidence of the presence of this disease.

One sign that is extremely helpful and that will definitely establish the diagnosis is the development of a cardiac murmur indicative of organic valvular disease. Ruegsegger [8] found that in 7 of his 19 patients aortic incompetency developed during their illness. The long, blowing murmur of aortic insufficiency developed in 11 of 16 patients of the present series. The time at which this murmur was first heard varied from the second to the fifty-first day in the hospital. Aortic insufficiency developed in 6 of the 7 patients that were shown at necropsy to have vege-

tations isolated to that valve. It was heard in all but 1 patient in whom autopsy disclosed perforation of an aortic cusp (8 of 9 patients). In both of the patients on whom autopsy could not be performed because permission was denied and in the patient now under treatment aortic diastolic murmurs developed and persisted. Once established, the murmur did not wax or wane in intensity appreciably. A developing or changing systolic murmur of mitral insufficiency did not help in the diagnosis of the condition of any patient in this series, in spite of the fact that autopsy disclosed 1 patient to have ulceration and fenestration of a mitral cusp. In no instance did the low-pitched, rumbling, crescendo murmur characteristic of mitral stenosis develop as in the case reported by Scott,[15] in which the vegetations on the mitral valves actually produced an effective stenosis.

The development of the murmur of aortic incompetency is so common that it must be regarded as a diagnostic feature of this disease. In every case of pneumococcic infection in which recovery is not rapid and complete the physician should make a painstaking search for this murmur with a diaphragm stethoscope over the entire precordium. Repeated readings of the blood pressure may give the first indication that aortic insufficiency has developed, by showing lowered diastolic pressure and increased pulse pressure. This should serve to make cardiac auscultation even more thorough.

THERAPY

Prevention, not cure, must be the goal in the therapy of pneumococcic endocarditis—prevention by means of early recognition and adequate treatment of pneumococcic infections. For the results of any treatment are disappointing once valvulitis has developed. Indeed, the physician has little to offer but continued endeavor. The sulfonamide drugs have seemingly made no difference in the uniformly fatal outcome of these cases, and added serum therapy has not been demonstrated to be efficacious. Penicillin perhaps will offer a new and potent form of therapy. The general measures for the care of the patient are in no way distinctive and need no discussion here.

Apparent cures have occurred. Wells,[16] Preble[17] and Laubry and Coffin[18] have all reported cases which seem clinically to have been instances of this disease and in which recovery took place. In these cases acute endocarditis with development of aortic insufficiency and embolic phenomena followed what was diagnosed as lobar pneumonia. In all cases the cardiac murmur persisted. Blumberg, Heine and Lipshutz[18] have recently reported a case in which there were multiple embolic manifestations, meningitis, a loud, harsh systolic apical murmur and growth of pneumococci, type XXVIII, in blood cultures on the thirty-sixth day of the patient's hospitalization. The positive blood cultures were obtained after the meningitis had cleared and after protracted treatment with both sulfadiazine and sulfathiazole and after many previous blood cultures had failed to reveal either aerobic or anaerobic organisms. Five hundred and forty thousand units of type-specific serum was given in the first seven days after the blood culture became positive, and administration of sulfathiazole was continued. More recently Keefer[19] has reported a cure with penicillin. In this instance acute endocarditis followed lobar pneumonia, and the murmur of aortic insufficiency developed during the course of the therapy. The murmur persisted after the patient's recovery. Loewe, Rosenblatt, Greene and Russell[20] have added the sixth apparent cure, that of a child with congenital heart disease whose blood culture showed growth of pneumococci, type XXVII, and who had pulmonary infarcts. Combined penicillin and heparin therapy was used.

SUMMARY

Pneumococcic endocarditis occurs in about 3 to 3.5 per cent of all pneumococcic infections and is responsible for probably about 5 to 10 per cent of deaths due to pneumococcic infections. The aortic and mitral valves are infected in 36 and

15. Scott, T.: Pneumococcic Endocarditis: A Report of Two Cases with Some Unusual Features, Internat. Clin. **2**:223 (June) 1941.

16. Wells, E. F.: Endocarditis as a Complication of Pneumonia, J. A. M. A. **39**:978 (Oct. 18) 1902.

17. Preble, H. B.: Pneumococcus Endocarditis, Am. J. M. Sc. **128**:782 (Aug.) 1904.

18. Laubry and Coffin, cited by Blumberg, N.; Heine, W. I., and Lipshutz, J.: Pneumococcus (Type XXVIII) Endocarditis with Recovery, J. A. M. A. **120**:607 (Oct. 24) 1942.

19. Keefer, C. S.; Blake, F. G.; Marshall, E. K.; Lockwood, J. S., and Wood, W. B.: Penicillin in the Treatment of Infections, J. A. M. A. **122**:1217 (Aug. 28) 1943.

20. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **124**:144 (Jan. 15) 1944.

33 per cent of the cases respectively. In only approximately 11 per cent of the cases are the valves of the right side of the heart solely involved. Antecedent valvular damage is present in a minority of the instances but is present often enough—perhaps in one third of the cases—that it may well contribute to the development of this disease. Purpura, splenomegaly and infarction of organs by emboli are less common than in subacute bacterial endocarditis. The ulcerative infectious process often produces fenestration of a valve cusp, with subsequent appearance of the murmur of aortic insufficiency. A thorough search for this murmur should be made in every case of pneumococcic infection which does not give evidence of rapid and complete recovery. Pneumococcemia is almost invariably present, and repeatedly positive blood cultures are presumptive evidence of the existence of this disease. The disease is usually rapidly fatal and may terminate in acute purulent meningitis. Treatment has so far been highly unsatisfactory.

BRONCHIECTASIS FOLLOWING ATYPICAL PNEUMONIA

MAJOR EARLE B. KAY
MEDICAL CORPS, ARMY OF THE UNITED STATES

During the past year 45 patients have been treated for bronchiectasis. The symptoms in 20 of these patients followed attacks of atypical pneumonia occurring during the winter of 1942-1943. It is with these 20 patients whose bronchiectasis appears to have been related to atypical pneumonia that this paper is primarily concerned. In 3 of the 20 patients, the bronchiectasis appeared to be reversible as confirmed by subsequent bronchograms. These 3 patients showed less severe cylindric bronchiectasis, confined mainly to the larger bronchi. The remaining 17 patients had more extensive bronchial and bronchiolar destruction, and the damage appeared to be permanent. The diagnosis of atypical pneumonia was made at the time of the original illness, prior to transfer to this hospital, and was concurred with only after careful reexamination of the clinical records and roentgenograms. It is impossible, with the material available to us to determine the general incidence of bronchiectasis following atypical pneumonia, for only the patients for whom this diagnosis was already established or suggested or who had persistent evidence of unresolved pneumonia were transferred.

Prior to pneumonia these patients had no symptoms relative to the pulmonary system. The roentgenograms made at the time of the patients' induction were obtained, reexamined and found to be entirely within normal limits. The attacks of atypical pneumonia were typical for this condition in every respect except that they failed to show spontaneous healing in the usual period. After the acute episode subsided, a cough remained which became increasingly productive. Basilar rales persisted in the affected lungs. Serial roentgenograms showed an unresolved pneumonia. These signs and symptoms continued for a number of months, and the presence of bronchiectasis was confirmed by bronchography.

Eight additional patients with bronchiectasis also claimed attacks of pneumonia in the Army to be the precursor of their cough and sputum. However, 6 of these patients gave histories of pneumonia during childhood, and reexamination of 5 of the 8 induction roentgenograms revealed suggestive evidence of pathologic pulmonary conditions existing at that time. One must be careful in stating that the attack of so-called atypical pneumonia was the precursor of the bronchiectasis and not in itself atypical because of preexisting bronchiectasis.

The remaining 17 patients with bronchiectasis either had vague histories as to the onset and duration of symptoms or fell into the more common group of persons whose symptoms had been present for years. The majority of these patients had had several attacks of pneumonia. The induction roentgenograms suggested the presence of bronchiectasis in many instances.

Bronchiectasis is a chronic disease characterized by persistent cough, foul sputum and general debility. The symptoms are usually present for a number of years before medical relief is sought. Perry and King [1] stated that 42 per cent of their 167 patients with bronchiectasis dated the onset of the disease to the first decade of life. Similar percentages have been recorded by other observers. Farrell [2] listed 54 per cent, Ogilvie [3] 66 per cent, Ballon, Singer and Graham [4] 54 per cent and Riggins [5] 41 per cent of their patients as having had the onset at this time. The majority of the remaining patients dated the onset of their symptoms of bronchiectasis from three to ten years prior to being seen by these authors and frequently considered their condition to be a result of previous attacks of pneumonia or infections of the respiratory tract. It is rare for patients with bronchiectasis to be seen whose cough, sputum and general debility have been of only several months' duration.

1. Perry, K. M. A., and King, D. S.: Bronchiectasis: A Study of Prognosis Based on a Follow-Up of 400 Patients, Am. Rev. Tuberc. **41**:531-548 (May) 1940.

2. Farrell, J. T.: The Importance of Early Diagnosis in Bronchiectasis, J. A. M. A. **106**:92-96 (Jan. 11) 1936.

3. Ogilvie, A. G.: Natural History of Bronchiectasis: Clinical, Roentgenologic and Pathologic Study, Arch. Int. Med. **68**:395-465 (Sept.) 1941.

4. Ballon, H.; Singer, J. J., and Graham, E. A.: Bronchiectasis, J. Thoracic Surg. **1**:154-193 (Dec.) 1931.

5. Riggins, H. M.: Bronchiectasis: Morbidity and Mortality of Medically Treated Patients, Am. J. Surg. **54**:50-66 (Oct.) 1941.

The shortness of the interval between the pneumonia and the onset of symptoms suggestive of bronchiectasis in this group, the fact that as far as could be ascertained there were no symptoms to suggest bronchiectasis prior to the pneumonia and the additional factor of normal roentgenograms taken at the time of induction into the Army stimulated my interest as to whether bronchiectasis could actually result from atypical pneumonia. With the easily available facilities of Army hospitals, bronchograms were made soon after the onset of symptoms suggestive of bronchiectasis. This may account for the short duration of symptoms between the attack of pneumonia and the diagnosis of bronchiectasis in these patients. If bronchographic examinations had been done earlier in other series of patients, the duration of symptoms prior to such a diagnosis would undoubtedly have been materially shortened.

It must be stated at the beginning that there is only one sure means of ascertaining the presence or absence of bronchiectasis, and that is bronchography. Since none of these patients had had bronchographic examinations prior to the onset of atypical pneumonia, it cannot be stated with certainty that they did not have preexisting bronchiectasis. One can only say that there was no reason to suspect this condition of having preexisted.

The purpose of this paper is the presentation of evidence to show that atypical pneumonia may present the factors frequently considered in the pathogenesis of bronchiectasis, namely, bronchial infection and obstruction. Case histories of patients having bronchiectasis following atypical pneumonia will be presented, with their serial bronchograms and pathologic observations. It is difficult to evaluate the role of the secondary bacterial invaders following in the path of the atypical pneumonia in the genesis of bronchiectasis, but it is felt that the atypical pneumonia is at least the initiating factor.

ATYPICAL PNEUMONIA

A knowledge of the fundamental aspects of atypical pneumonia is essential to an understanding of the processes involved in the development of bronchiectasis. Bowen [6] was among the first to recognize atypical pneumonia as a new disease entity. He described this condition as being an "acute influenzal pneumonitis," a benign type of bronchopneumonia occurring in soldiers stationed in Hawaii. Allen [7] in 1936 characterized the disease as an "acute interstitial pneumonitis." Others [8] have considered it to be a viral pneumonia. No attempt will be made to discuss the causation. Suffice it to say that the majority of observers believe that the condition, in the present state of knowledge, is best named "primary atypical pneumonia, etiology undetermined." The disease has epidemic potentialities and may cause illness of varying severity up to and including death. Whether this is a new disease entity or not is probably still open to question. A review of the literature shows that there are a number of etiologic agents capable of producing this clinical picture. Similarly, influenzal bronchopneumonia as seen in World War I has been described as an atypical pneumonia by a number of observers.[9] Certainly, atypical pneumonia as described today in its more severe and protracted forms is similar in many respects to influenzal bronchopneumonia, except that the latter condition in the epidemic form appeared to be more virulent and associated with a higher mortality. It will be remembered that pathologically bronchiectatic bronchi were not an uncommon condition following that disease.

Atypical pneumonia is usually described [10] as a mild to a moderately severe illness affecting

6. Bowen, A.: Acute Influenza Pneumonitis, Am. J. Roentgenol. **34**:168-174 (Aug.) 1935.

7. Allen, W. H.: Acute Pneumonitis, Ann. Int. Med. **10**:441-446 (Oct.) 1936.

8. (*a*) Adams, J. M.; Greene, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: Comparative Study of Two Epidemics, J. Pediat. **20**:405-420 (April) 1942. (*b*) Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: Disease Entity Probably Caused by a Filtrable Virus, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938. (*c*) Reimann, H. A.; Havens, W. P., and Price, A. H.: Etiology of Atypical ("Virus") Pneumonias, Arch. Int. Med. **70**:513-522 (Oct.) 1942. (*d*) Reimann, H. A.: Viral Pneumonias, Bull. New York Acad. Med. **19**: 177-181 (March) 1943.

9. Norris, G. W., and Landis, H. R. M.: Diseases of the Chest and the Principles of Physical Diagnosis, ed. 4, Philadelphia, W. B. Saunders Company, 1931.

10. (*a*) McCarthy, P. V.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:344-346 (April) 1943. (*b*) Haight, W. L., and Trolinger, J. H.: Primary Atypical Pneumonia, Etiology Unknown, U. S. Nav. M. Bull. **41**:988-1000 (July) 1942. (*c*) Dingle, J. H.; Abernethy, T. J.; Badger, G. F.; Buddingh, G. J.; Teller, A. E.; Langmuir, A. D.; Ruegsegger, J. M., and Wood, B. W.: Primary Atypical Pneumonia, Etiology Unknown, War Med. **3**:223-248 (March) 1943. (*d*) Zimmerman, J. J.: Viral Pneumonia, Am. J. Nursing **43**:141-144 (Feb.) 1943. (*e*) Smiley, D. F.; Showacre, E. C.; Lee, W. F., and Ferris, H. W.: Acute Interstitial Pneumonitis: A New Disease Entity, J. A. M. A. **112**:1901-1904 (May 13) 1939. (*f*) Murray, M. E., Jr.: Atypical Bronchopneumonia of Unknown Etiology Possibly Due to Filterable Virus, New England J. Med. **222**:565-573 (April 4) 1940. (*g*) Suttenfield, F. D.: Primary Atypical Pneumonia (Virus Pneumonia), Mil. Surgeon **93**:360-364 (Oct.) 1943. (*h*) Grieco, E. H.; Cove, A. M., and Klein, E. C.: Pneumonia: A Survey of One Hundred and Six Cases, ibid. **93**:364-367 (Oct.) 1943.

young adults, persisting from five to fourteen days and uninfluenced by chemotherapy. The onset is insidious in some patients, while in others the illness begins with an acute nasopharyngitis, a dry cough that is occasionally productive, chills or chilly sensations, headaches, night sweats and general malaise. Some patients are able to continue work for four or five days prior to hospitalization, while others are admitted in twenty-four to forty-eight hours with a temperature elevated to 102 to 104 F. Usually the pulse and respiratory rates are low in comparison to the fever, but an occasional patient is intensely dyspneic and even cyanotic. The fever usually subsides in three to five days by lysis. There is a normal leukocyte count early, and a secondary rise to 12,000 to 18,000 in a week to ten days.

The changes in the chest shown on physical examination are minimal in comparison to the extent of the disease shown roentgenographically. Often there are no abnormal conditions in the chest on admission, but after two or three days dulness over the affected site, impaired or decreased breath sounds and rales are noted. As the temperature falls, coarse rales are frequently noted to increase in numbers, and in many patients they first become noticeable during this period of defervescence. Rarely do patients show evidence of tubular breathing, as expected when there is pneumonic consolidation. There is often a great disproportion between the relatively mild clinical signs and symptoms and the roentgen observations. This suggests that the underlying process may be largely atelectatic rather than entirely infectious. Furthermore, the fact that frequently the roentgen changes precede the physical changes raises the question as to whether or not the original lesion is relatively minimal but sufficient to produce lobular atelectasis and whether the rales and impaired breath sounds later noted are secondary to the atelectasis.

Examinations of the sputum for the most part show only the normal inhabitants. Approximately 15 per cent of patients have bloody sputum. Rhoads [11] expressed the belief that Streptococcus viridans, which was present in most of his cases, contributed to the death of 1 patient. Others have considered that such organisms are secondary invaders and of no importance. Kneeland and Smetana [12] reported only the usual bacterial flora, such as nonhemolytic streptococci, Str. viridans, Staphylococcus albus, Staphylococcus aureus and gram-negative cocci. Hemolytic streptococci and Haemophilus influenzae are inconspicuous. Occasionally higher types of pneumococci which cannot be typed are found. They stated that secondary bacterial infection of the lungs occurs rarely.

Others [13] described a more severe and prolonged form of the disease occurring along with the milder forms in the same epidemic and in a few instances ending in death. The more severe form, as would be expected, shows more extensive pulmonary changes both on physical and on roentgen examination. The onset and course in this form are similar to those of the milder form for the first week or so. The patients then become more critically ill and have a severe cough, which is frequently productive. They are dyspneic, cyanotic and exhausted. The temperature is elevated from 104 to 105 F. for a number of days. Continuous oxygen therapy and repeated transfusions are necessary. The pneumonia is usually bilateral and shows a tendency to migrate. The course is longer, and in some instances the disease persists for months.

Reimann [8b] described the infection as spreading rapidly in some cases and more slowly in others until the trachea, bronchi and eventually the lungs are involved in a diffuse, bilateral process which persists for several weeks and is followed by a residuum lasting several months. There is involvement of much of the bronchiolar system as manifested by dyspnea and cyanosis, but consolidation is never striking. Kneeland and Smetana [12] described the presence of obstructed breathing which may be associated with areas of atelectasis. Some of their patients, they stated, gave the picture of extreme pulmonary insufficiency and were cyanotic even in high concentrations of oxygen. Recently in a review of 1,862 cases of atypical pneumonia by van Ravenswaay and

11. Rhoads, P. S.: The Probable Incidence and Clinical Features of "Virus" Pneumonia, Radiology **40**:327-338 (April) 1943.

12. Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**:229-268 (Oct.) 1940.

13. (*a*) Correll, H. L., and Cowan, I. I.: Primary Atypical Pneumonia, U. S. Nav. M. Bull. **41**:981-987 (July) 1943. (*b*) Hufford, C. E., and Applebaum, A. A.: Atypical Pneumonia of Probable Virus Origin, Radiology **40**:351-359 (April) 1943. (*c*) Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X), Bull. Johns Hopkins Hosp. **67**:268-305 (Oct.) 1940. (*d*) van Ravenswaay, A. C.; Erickson, G. C.; Reh, E. P.; Siekierski, J. M.; Pottash, R. R., and Gumbiner, B.: Clinical Aspects of Primary Atypical Pneumonia, J. A. M. A. **124**:1-6 (Jan. 1) 1944. (*e*) Reimann.[8b] (*f*) Reimann, Havens and Price.[8e] (*g*) Reimann.[8d] (*h*) Smiley, Showacre, Lee and Ferris.[10e] (*i*) Grieco, Cove and Klein.[10h] (*j*) Kneeland and Smetana.[12]

co-workers,[13d] the increasing virulence of atypical pneumonia was stressed. Recurrence of the pneumonia in patients allowed up too soon was as high as 23.3 per cent. An additional 18.5 per cent had other complications, such as pleural fluid, empyema, chronic bronchitis and bronchiectasis.

Roentgen Observations.—The roentgen signs of atypical pneumonia usually do not appear until the fourth day,[10a] are less dense than are seen in part of the chest but is most commonly seen in the right cardiophrenic angle. The mottled type of densities is interpreted as a lobular form of atelectasis based on a mechanical factor, the complete block of the smaller bronchi and bronchioli by exudate and swollen epithelium. Correll and Cowan [13a] described two fairly frequent types: one in which the roentgenogram reveals a dense circumhilar shadow with a fanlike infiltration into the surrounding pulmonary tissue, and a

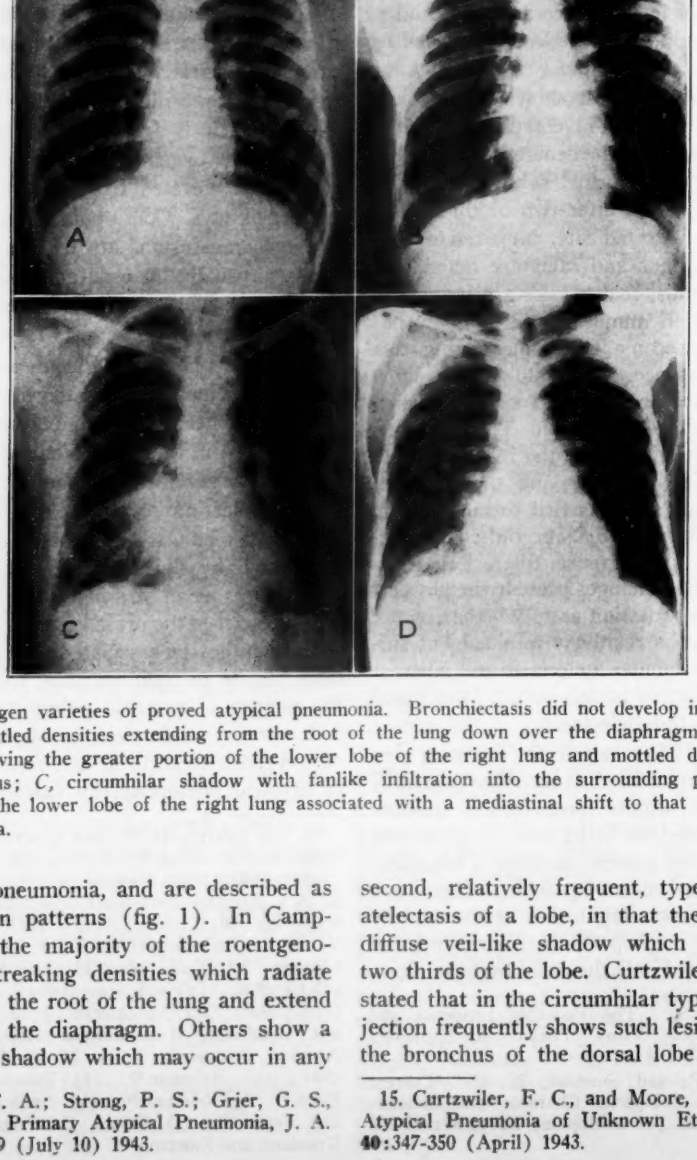

Fig. 1.—Roentgen varieties of proved atypical pneumonia. Bronchiectasis did not develop in these cases. *A*, streaking and mottled densities extending from the root of the lung down over the diaphragm; *B*, diffuse veil-like shadow involving the greater portion of the lower lobe of the right lung and mottled density in the left costophrenic sulcus; *C*, circumhilar shadow with fanlike infiltration into the surrounding pulmonary tissue; *D*, atelectasis of the lower lobe of the right lung associated with a mediastinal shift to that side in a case of atypical pneumonia.

cases of lobar pneumonia, and are described as following certain patterns (fig. 1). In Campbell's [14] series, the majority of the roentgenograms reveal streaking densities which radiate downward from the root of the lung and extend over the leaf of the diaphragm. Others show a mottled type of shadow which may occur in any second, relatively frequent, type suggestive of atelectasis of a lobe, in that there is usually a diffuse veil-like shadow which occupies about two thirds of the lobe. Curtzwiler and Moore [15] stated that in the circumhilar type a lateral projection frequently shows such lesions to be along the bronchus of the dorsal lobe rather than at

14. Campbell, T. A.; Strong, P. S.; Grier, G. S., and Lutz, R. J.: Primary Atypical Pneumonia, J. A. M. A. **122**:723-729 (July 10) 1943.

15. Curtzwiler, F. C., and Moore, B. E.: Primary Atypical Pneumonia of Unknown Etiology, Radiology **40**:347-350 (April) 1943.

the hilus. They contended that the involvement is always along the distribution of a portion of the bronchial tree. Haight and Trolinger [10b] described four types: homogeneous, mottled, linear and a combination of the three. It was felt by them that the lesions usually retain their original appearance and do not spread or become confluent. This would suggest that the underlying lesion is mechanical (atelectasis) rather than wholly infectious (pneumonia). In contradistinction, Dingle and associates [10c] commented on the rapidity of the change in the roentgen appearance of the lesions over a period of a few days. Other observers [16] described the pneumonia as migratory. New foci of pneumonic infiltration may develop rapidly in other lobes and in the opposite lung. Multiplicity of lobes involved is reported in 10 to 20 per cent of cases. McCarthy [10a] and Campbell [14] described as one of the roentgen varieties parenchymal areas of infiltration resembling tuberculosis.

Pathologic Aspects.—Deaths from this disease are rare; consequently pathologic data are scarce. Most of the patients in whom death occurred died as a result of preexisting complicating heart and kidney diseases. The significant pathologic findings in the reported deaths will be summarized.

Kneeland and Smetana [12] reported 1 death in 52 cases. The microscopic appearance of the lungs showed occasional septums to be thickened by fibrous tissue and infiltrations consisting of mononuclear wandering cells and polymorphonuclear leukocytes. Some alveoli showed large mononuclear cells arranged in rows about the periphery. An occasional hyaline membrane was present. The mucosa of the larger bronchi and of the trachea was densely infiltrated by polymorphonuclear leukocytes and mononuclear wandering cells. Their epithelial lining cells were prominent and frequently projected into the lumens in the form of small papillae. Some of the lumens contained mucopurulent exudate and debris. In summary, the alveoli, interstitium and bronchi were the areas affected by this disease. The anatomic diagnosis was lobular pneumonia with organization and acute tracheobronchitis.

One death occurred in the 285 cases reported by Dingle and associates.[10c] Microscopically, the lungs showed congestion and infiltration of the alveolar walls with monocytes, lymphocytes, plasma cells and occasional neutrophils. A similar reaction was present in the perivascular and peribronchial interstitial tissues. The alveoli contained many large actively phagocytic monocytes, a moderate number of eosinophils, a scant number of neutrophils, fibrin, edema fluid and erythrocytes. The walls of the bronchi showed an acute inflammatory process with extensive ulceration of the bronchial mucosa; the lumens of the bronchi were plugged with an exudate composed chiefly of neutrophils. The conditions found were a hemorrhagic interstitial bronchopneumonia and an acute ulcerative bronchitis.

Campbell and co-workers [14] described 1 death among 200 patients. The microscopic examination revealed in the lungs bronchitis, bronchiolitis, peribronchitis and interstitial pneumonitis, and atelectasis secondary to the bronchiolitis and peribronchiolitis. The major bronchi showed sloughing of the epithelium. The mucosa was moderately edematous and diffusely infiltrated with lymphocytes, occasional plasma cells and a moderate number of neutrophils. The smaller bronchi showed a similar process with the lumens partly occluded by a purulent exudate. There was a conspicuous peribronchial accumulation of lymphocytes and plasma cells. There was a general decrease in the size of the alveoli. This process was associated frequently but not always with a thickening of the alveolar wall. The alveoli with thickened walls contained numerous cells. Many of the alveoli were atelectatic as a result of the bronchial plugs.

Longcope [13c] reported 32 cases of atypical pneumonia with 2 deaths. Both of these occurred in patients with preexisting chronic rheumatic heart disease. Microscopically the lungs showed the bronchi to be filled everywhere with a thick exudate consisting of about half polymorphonuclear leukocytes and half round cells. Their walls were everywhere infiltrated with round cells and occasional polymorphonuclear leukocytes. All the alveoli were solidly filled with round cells. There was almost complete absence of polymorphonuclear leukocytes everywhere except in the bronchi in 1 case, while in the other the peribronchial alveoli were similarly involved. The bronchial epithelium of the larger bronchi showed squamous metaplasia.

The pathologic changes of the patients dying from atypical pneumonia as described by McCarthy,[10a] Rhoads [11] and Saphir [17] were similar in most respects to those in preceding pathologic reports except that the interstitial nature of the

16. Haight and Trolinger.[10b] Rhoads.[11] Kneeland and Smetana.[12] Campbell, Strong, Grier and Lutz.[14] Correll and Cowan.[13a] Hufford and Applebaum.[13b] Longcope.[13c]

17. Saphir, O.: Pathological Changes in Atypical Pneumonia, Radiology **40**:339-343 (April) 1943.

process was more apparent than the evidence of bronchial and bronchiolar infection.

Adams [18] discussed the pathologic observations on 9 infants dying during an epidemic of 32 cases of viral pneumonia. Grossly, the pulmonary tissue was congested, with scattered areas of hemorrhagic bronchopneumonia. Exudate could be expressed from the bronchi and bronchioles. Microscopically, the outstanding pathologic features were necrosis and ulceration of the bronchial epithelium with a rather high degree of atelectasis in all cases. The bronchial and bronchiolar lumens were filled with sloughed epithelial cells. Patches of peribronchial infiltration were composed mainly of mononuclear cells. The edema, hemorrhage and swelling of the surrounding parenchymal tissues seemed to contribute to the collapse of the bronchiolar system. Polymorphonuclear leukocytes, lymphocytes and large mononuclear phagocytes were found in the alveolar spaces. Characteristic cytoplasmic inclusion bodies were found in the bronchial epithelium in all fatal cases occurring in this epidemic.

In summary, it is noted that clinically, roentgenologically and pathologically atypical pneumonia may present two factors commonly described in the pathogenesis of bronchiectasis, namely, bronchial and bronchiolar infection and occlusion as well as the more commonly recognized condition of interstitial pneumonitis. The bronchial occlusion, as manifested by areas of atelectasis, is demonstrated microscopically by the swollen, edematous and ulcerated mucous membrane and bronchial plugs of purulent exudate. The atelectatic feature of atypical pneumonia is demonstrated in the roentgenogram presented in figure 1 *D*.

THE ROLE OF BRONCHIAL OBSTRUCTION AND INFECTION IN THE PRODUCTION OF BRONCHIECTASIS

Many theories have been advanced regarding the cause and pathogenesis of bronchiectasis. Some authors still emphasize the congenital nature of the disease, but the majority at the present time believe that bronchiectasis is acquired. The correlation between bronchial infection and obstruction with resulting atelectasis, and the subsequent development of bronchiectasis as demonstrated by careful analysis of case records, serial roentgenograms and postmortem examinations has suggested this pathogenesis. This relationship was first noted in cases of foreign bodies present in the bronchial tree.

Anspach [19] was among the first to stress the fact that an unrelieved basal triangular shadow indicative of atelectasis following bronchopneumonia in infants is important in the production of bronchiectasis. He added that only too often the patient is discharged from the hospital before the roentgen conditions have cleared or before additional roentgenograms have been taken, even though the temperature is essentially normal. He stated that in infants a collapsed lower lobe that remains atelectatic will reveal some evidence of bronchial dilatation within six weeks to two months. Anspach [19b] was able to follow 100 consecutive patients presenting a small basal triangular roentgen shadow, the majority for a number of years. Eleven died and came to necropsy. Nine of these deaths occurred in infancy, within a few weeks after the first pulmonary symptoms. From necropsy studies and also as a result of following other patients with serial roentgenograms over a period of years, he stated that it is the bronchial or bronchiolar obstruction with resulting atelectasis that accounts for the triangular shadow and that under certain conditions it may be the precursor of the bronchiectasis and not merely an associated finding.

Tannenberg and Pinner,[20] in an attempt to clarify the causative role that bronchial obstruction plays in the development of bronchiectasis, performed a number of animal experiments, producing bronchial obstruction by intrabronchial and extrabronchial methods. Simultaneously, in part of the experiments a pneumothorax on the operative side was produced, to determine whether or not the loss of the usually high negative intrapleural pressure encountered in atelectasis was the actual force causing the bronchi to dilate. Definite evidence of bronchial dilatation and saccular bronchiectasis with roentgen evidence of atelectasis were found in rabbits dying not earlier than two weeks after the operation. The most extensive bronchiectasis was noted in rabbits which died between the twenty-fifth and the thir-

18. Adams, J. M.: Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies, J. A. M. A. **116**:925-933 (March 8) 1941.

19. Anspach, W. E.: (*a*) Atelectasis and Bronchiectasis in Children: A Study of Fifty Cases Presenting a Triangular Shadow at the Base of the Lung, Am. J. Dis. Child. **47**:1011-1051 (May) 1934; (*b*) Bronchiectasis, Collapsed Lung, and the Triangular Basal Shadow in the Roentgenogram, and Their Inter-Relationship, Am. J. Roentgenol. **41**:173-183 (Feb.) 1939; (*c*) Roentgenologic Aspects of Bronchiectasis, Dis. of Chest **9**: 24-38 (Jan.) 1943.

20. Tannenberg, J., and Pinner, M.: Atelectasis and Bronchiectasis: An Experimental Study Concerning Their Relationship, J. Thoracic Surg. **11**:571-616 (Aug.) 1942.

tieth postoperative day. The presence and maintenance of a pneumothorax on the obstructed side did not essentially alter the final result; it did not prevent the formation of bronchiectasis. "Death of many of the rabbits was caused apparently by a contralateral bronchopneumonia, probably the result of intrabronchial aspiration of exudate from the bronchiectatic lung," but such areas of bronchopneumonia when uncomplicated by bronchial obstruction never became bronchiectatic. Similarly, when the bronchial obstruction was not associated with bronchial infection distal to the point of obstruction or when the obstruction had not become complete, as a result of a localized area of bronchial dilatation at the site of the obstructing agent sufficient to allow bronchial drainage, bronchiectasis did not result. These experiments suggest that bronchial obstruction and infection are both necessary in the development of bronchiectasis. A coexisting pneumothorax did not alter the result. This confirms Andrus'[21] previous experiments and his assertion that increased negative pressure of the pleural space does not exert any significant dilating stress in the presence of atelectasis.

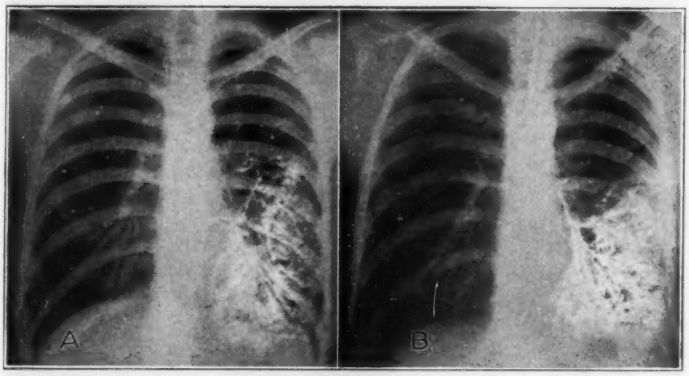

Fig. 2.—Reversible bronchiectasis in a patient with atypical pneumonia in September 1943 and again in January 1944. Because of symptoms suggestive of bronchiectasis, bronchograms were made on March 15 (*A*), which revealed cylindric bronchiectasis confined primarily to the larger bronchi. After clinical improvement during the next four months bronchography was repeated on July 1 (*B*), revealing no bronchiectasis. A bronchogram of the right side was normal.

RELATIONSHIP OF ATYPICAL PNEUMONIA TO BRONCHIECTASIS

So far it has been shown that bronchial and bronchiolar infection and occlusion may occur in atypical pneumonia. Furthermore, other authors have shown both clinically and experimentally that these two factors may produce bronchiectasis. Therefore, when a number of patients have been seen in whom symptoms suggestive of bronchiectasis develop following a protracted course of atypical pneumonia, this cause and effect relationship should be considered.

In an attempt to determine the permanency and extent of the bronchial and bronchiolar damage in the 20 cases of bronchiectasis attributable to atypical pneumonia, bronchography was repeated over a period of two to six months. In only 3 instances in this small series were bronchiectatic bronchi noted to resume their normal contour and show evidence of clearing (fig. 2). The bronchiectasis in the remaining 17 patients appeared to be permanent. Because of persistent clinical symptoms as well as bronchographic evidence of bronchiectasis, 10 of these 17 patients have had lobectomies. The interval between the acute episode of atypical pneumonia and the operation varied from six to thirteen months. As will be noted later in the case presentations, there was pathologic verification of the irreparable bronchiectatic damage to the bronchial tree in the lobes resected, substantiating the permanency of the bronchial destruction by the previous disease process. Blades and Dugan[22] have reported pseudobronchiectasis following atypical pneumonia which cleared spontaneously within two to three months of the acute disease. Reversible bronchiectasis (pseudobronchiectasis) as noted in my 3 cases may occur if the bronchial and bronchiolar destruction produced by the disease process has not been sufficient to produce irreparable damage to the bronchial walls. All gradations of bronchial and bronchiolar damage

21. Andrus, P. M.: Bronchiectasis: An Analysis of Its Causes, Am. Rev. Tuberc. **36**:46-79 (July) 1937.

22. Blades, B., and Dugan, D. J.: Pseudobronchiectasis Following Atypical Pneumonia, Bull. U. S. Army M. Dept., November 1943, no. 70, pp. 60-68.

may result, depending on the severity and the duration of the disease process. Bronchographically such bronchial dilatation is usually cylindric and confined to the larger bronchi. Only repeated bronchographic examinations over a period of months will determine when bronchiectasis is permanent and when it is reversible. The decision as to operation should be postponed until an established diagnosis is made.

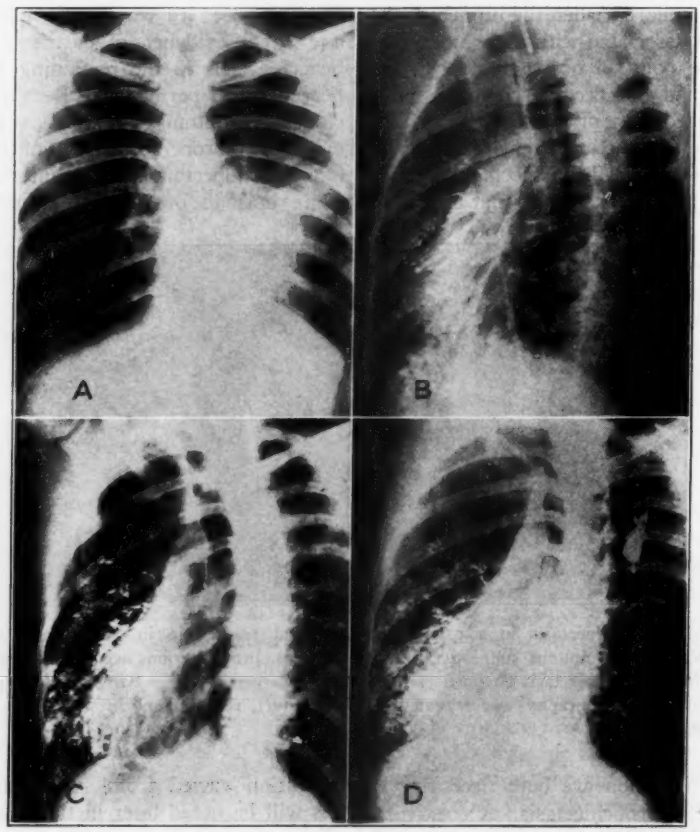

Fig. 3.—Roentgenogram and serial bronchograms over a period of four months of a patient having atypical pneumonia in which the roentgen and physical abnormalities persisted over a longer period than usually noted. *A*, roentgenogram demonstrating a residual pneumonitis in the lingula of the left lung, the site of involvement by atypical pneumonia; *B*, a right anterior oblique bronchogram demonstrating the bronchi of the lingula to be slightly dilated and more closely crowded together and to have blunted ends—probably indicative of inspissated exudate in an atelectatic lingula; *C* and *D*, serial right anterior oblique bronchograms over a four month period demonstrating gradual return to normal of the lingular bronchial tree and filling by iodized poppyseed oil of this bronchial segment. Physical abnormalities also disappeared at this time.

Bronchographic examinations were performed on 15 additional patients who had had atypical or viral pneumonia from one to four months previously. In some of these patients the course of the atypical pneumonia had been somewhat protracted, rales had persisted or there had been roentgen evidence of atelectasis or unresolved pneumonia for some time. In the majority of these cases, however, the course had been essentially uncomplicated. The abnormal roentgen conditions in this group had completely disappeared prior to bronchography in all but 2 cases. Except in these 2 cases the bronchograms were normal. These 2 cases are examples of less severe bronchial damage resulting from atypical pneumonia and might be considered as intermediate stages in the development of bronchiectasis.

The first patient was an 18 year old white youth who was hospitalized July 5, 1943 for atypical pneumonia. The temperature on admission was 103 F., and the white blood cell count was 8,000. Roentgenograms taken two days after admission showed pneumonitis extending out from the left hilus (fig. 3 *A*), but rales were not heard until after one week. The temperature became normal within a week and the patient felt considerably better, but a nonproductive cough persisted for about two months, associated with weakness and loss of weight. Rales could be heard during this time

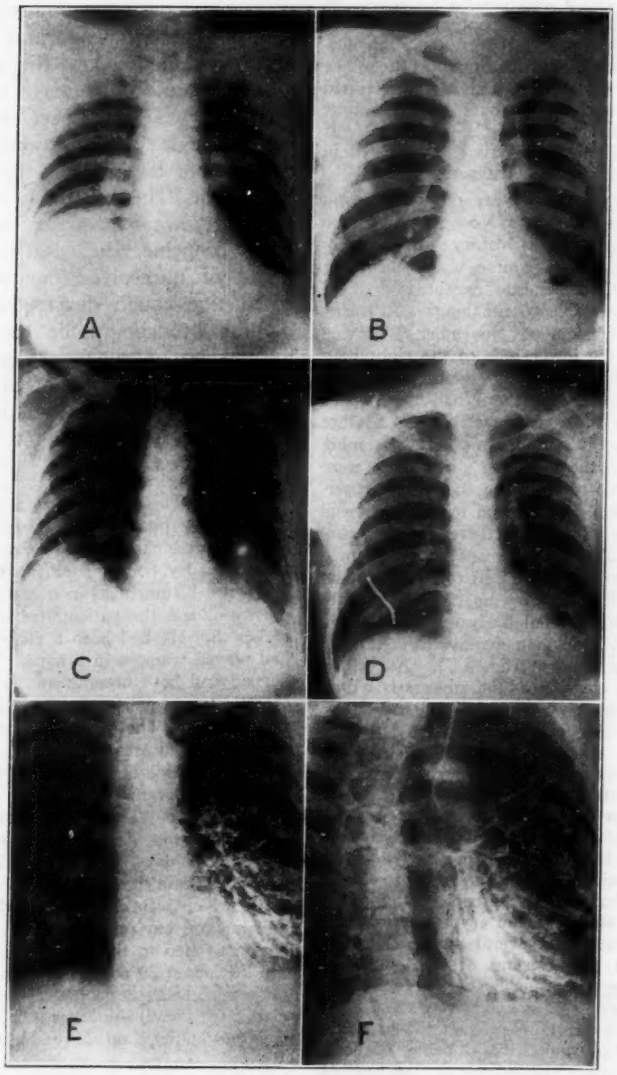

Fig. 4.—Serial roentgenograms and bronchograms of a patient having atypical pneumonia persisting over a longer period than usually noted and giving rise to damaged, dilated and distorted bronchi and bronchioli of the lower lobe of the left lung. *A*, roentgenogram demonstrating elevation of the right side of the diaphragm associated with atelectasis of the lower lobe of the right lung during an acute episode of atypical pneumonia. *B*, roentgenogram showing spontaneous improvement of the atelectasis within one week. There is also noted roentgen evidence of pneumonitis in the lower lobe of the left lung and beginning obliterative pleuritis of the left costophrenic gutter. *C*, a roentgenogram one month later demonstrating a recurrence of the atelectasis of the right lower lobe with elevation of the right side of the diaphragm. Again, there was spontaneous improvement within one week's time. There was increase in the pneumonitis of the left lower lobe over that noted in the roentgenogram one month previously (*B*). *D*, persistence of the pneumonitis of the left lower lobe for an additional month. The right side had remained clear. *E*, bronchogram demonstrating evidence of bronchial and bronchiolar damage, dilatation and distortion by the pneumonic process. Additional bronchograms revealed the right bronchial tree to be normal. *F*, right anterior oblique bronchogram repeated after a seven week interval demonstrating slight increase in the bronchial dilatation. Additional bronchograms will subsequently be obtained to see whether this process is progressive, stationary or reversible.

over the lingular area. Serial roentgenograms revealed unresolved pneumonia and a questionable atelectasis of the lingula for a period of several months. The initial bronchogram (fig. 3 *B*) demonstrated an atelectatic lingula with dilated bronchi that were crowded together and had blunted ends—probably a result of inspissated exudate. Repeated bronchograms over the next four months showed gradual clearing (fig. 3 *C* and *D*). If the bronchial occlusion and atelectasis had persisted in this case, bronchiectasis might have resulted.

The second patient was a 51 year old officer who was hospitalized for two weeks in November 1943 for atypical pneumonia. The past history was entirely noncontributory. His clinical course was typical for atypical pneumonia in all respects except that there were few symptoms referable to the lungs. A roentgenogram of the chest taken on November 9 showed massive atelectasis of the lower lobe of the right lung with an elevated diaphragm and mediastinal shift (fig. 4 *A*). By November 16, there had been spontaneous clearing of the lobar atelectasis (fig. 4 *B*), but as noted in this roentgenogram there was a beginning obliterative pleuritis on the left side. Still there were no significant symptoms referable to the chest proper. The patient was returned to duty and felt entirely well until December 19, at which time there was a recurrence of symptoms. There was a severe cough productive of 4 to 5 ounces (120 to 150 cc.) of purulent sputum daily and an elevation of temperature to 104 F. for four days that gradually fell by lysis. The patient was again hospitalized, and again massive atelectasis of the right lower lobe was noted (fig. 4 *C*). As before, there was spontaneous clearing of the atelectasis within a week. However, a new pneumonic process was noted in the base of the lower lobe of the left lung in the roentgenograms taken December 19. Also there was an increase in the obliterative pleuritis, resulting in an elevation and flattening of the diaphragm on the left side. This process in the left lower lobe persisted for the next month (fig. 4 *D*) associated with basilar rales on this side. However, the productive cough disappeared. The patient then transferred to Percy Jones General Hospital. Bronchoscopic examination performed Jan. 24, 1944 showed an erythematous granular mucous membrane with several small superficial areas of ulceration in the bronchus of the lower lobe of the left lung, while the bronchus of the lower lobe of the right lung showed rather extensive ulceration of an acute nature with some diminution of the bronchial lumen. Because of the suggestive evidence of bronchiectasis, bronchograms were taken on January 31. Damaged, dilated and somewhat distorted bronchi and bronchioli as noted in the bronchograms (fig. 4 *E*) were found. The progressive obliterative pleuritis and the distortion and dilatation of the bronchi of the lower lobe of the left lung over a period of two months as noted roentgenologically suggested that the underlying process might still be active. This probably resulted from a combination of bronchial destruction and an interstitial fibrosis. The patient was reexamined bronchoscopically on March 11, and complete healing of the previous ulcerative bronchitis was noted; however, bronchographic examination on March 21 (fig. 4 *F*) showed a slight increase in the bronchial dilatation. Subsequent bronchograms will be obtained later to determine whether this process is stationary, progressive or reversible.

Representative cases of patients acquiring bronchiectasis following attacks of so-called atypical pneumonia will now be presented. As previously stated, these patients were entirely free from pulmonary symptoms prior to the pneumonia—the roentgenograms taken at the time of their induction into the Army were normal. The symptoms and signs of the acute phase were typical in every respect, but the subsequent courses were either protracted or recurrent. The majority of the patients had multiple lobar involvement. The initial sites of the pneumonia were not always the areas later found to have become bronchiectatic. Rales and roentgen evidence of unresolved pneumonia persisted. A productive cough developed, and after several months bronchographic examinations revealed the presence of bronchiectasis. Repeated bronchograms in this group showed that the bronchiectasis was irreversible. This was further confirmed by the microscopic examination of the resected lobes.

Case 1.—This patient was a 31 year old white man who was hospitalized on Jan. 24, 1943 for a cold in the head and chest characterized by a temperature of 102 F., a dry cough, sore throat and general malaise. The past history was noncontributory. Prior to the present illness the patient had always been in the best of health. He had been a champion tennis player and had played trumpet in a band. During early childhood he had had both measles and whooping cough without complications. The induction roentgenogram (fig. 5 *A*) was normal. The physical examination revealed rales and diminished breath sounds at the base of both lungs. The white blood cell count was normal. Unfortunately, no roentgenograms of the chest were taken during this hospitalization. The temperature gradually returned to normal in three days, and the patient was returned to duty in five days. During the latter part of February 1943 he again noted a pharyngitis and tracheobronchitis which was associated with cough and increasing amounts of purulent sputum. This increased over a period of two to three months, but he continued duty. He lost about 20 pounds (9 Kg.) in weight during this period. Not until he had an acute exacerbation associated with chills did he seek medical attention. He was hospitalized on May 20, with a temperature of 103.5 F. and an elevation of leukocytes to 20,000. Physical examination at this time showed diminished breath sounds, dulness and rales at the base of both lungs posteriorly. Serial roentgenograms during the following three months showed multiple foci of bronchopneumonia in both the right and the left lung (fig. 5 *B*). After approximately one month, however, all but the basilar involvement showed resolution (fig. 5 *C*). Because of basilar pneumonitis, the persistent physical findings and the presence of a productive cough, bronchiectasis was suspected. Bronchograms were made August 9, which confirmed the clinical impression of bronchiectasis (fig. 5 *D*). The patient was then transferred to Percy Jones General Hospital. Six weeks later bronchography was repeated, and again there was revealed the presence of extensive cylindric and saccular bronchiectasis bilaterally. With conservative therapy the symptoms of bronchiectasis remained unabated over the next several months. A lobectomy of the lower lobe of the left lung was performed on November 10. The postoperative course was uneventful. Microscopically, sections of the removed lung

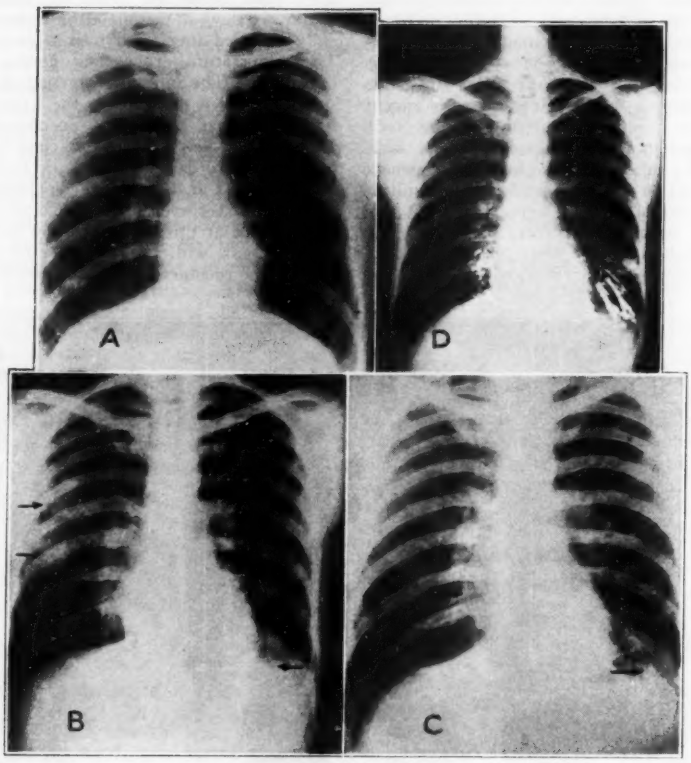

Fig. 5 (case 1).—Roentgenograms demonstrating the development of bronchiectasis in a case of atypical pneumonia. *A*, roentgenogram of a healthy chest at the time of induction into the Army. *B*, roentgenogram taken during the acute illness of atypical pneumonia, demonstrating the multiple foci of pneumonic involvement. *C*, roentgenogram taken one month after *B*, demonstrating persistence of the pneumonia at the right cardiophrenic angle and the base of the left lung. Evidence of unresolved pneumonia remained in these areas. *D*, bronchograms made prior to the patient's transfer to this hospital, demonstrating the development of bilateral basilar bronchiectasis at the sites previously illustrated as showing evidence of failure to resolve. Subsequent bronchograms showed no change in the degree of bronchiectasis.

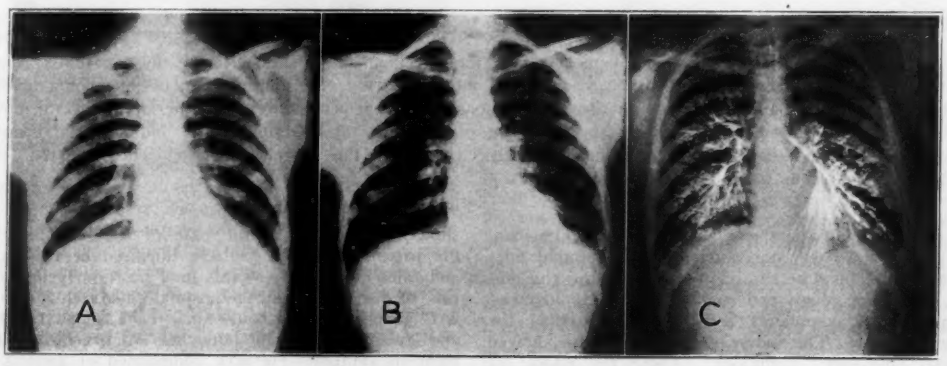

Fig. 6 (case 2).—Roentgenograms demonstrating the development of bronchiectasis in a case of atypical pneumonia. *A*, roentgenogram taken Feb. 12, 1943, demonstrating a new focus of pneumonia at the right cardiophrenic angle and a recurrence of the pneumonia at the base of the left lung. *B*, roentgenogram taken four months after the previous one, demonstrating the persistence of pneumonitis at the base of the left lung. *C*, bronchogram made Aug. 20, 1943, demonstrating the development of bronchiectasis at the previous site of unresolved pneumonia. Subsequent bronchograms showed no change.

tissue showed greatly dilated bronchi and bronchioli. There was pronounced inflammatory thickening of their walls and of the surrounding parenchyma. The lumens contained a purulent exudate. The epithelial lining was infiltrated with polymorphonuclear leukocytes. The muscularis could scarcely be identified as such except for short fragments of degenerated fibers. The connective tissue support was similarly incomplete, variable in amount and hyalinized. The largest component of the wall appeared to be the granulomatous infiltration. The peribronchial alveoli were atelectatic and densely infiltrated with lymphocytes and histiocytes. Many of the alveolar lumens were obliterated, and others were filled with a purulent exudate.

The white blood cell count on admission was 5,100, but in six days it became elevated to 27,900 and gradually subsided to normal over a period of two weeks. The temperature dropped to normal within seventy-two hours. The initial roentgenogram, on February 3, showed mottled densities in the lower lobe of the left lung suggestive of atypical pneumonia. By February 10, the chest was reported as clear roentgenologically, but within two days there was evidence of a new pneumonic process at the right cardiophrenic angle (fig. 6 *A*) as well as recurrence in the base of the left lung. The patient at this time clinically had an exacerbation of his illness, with a temperature of 104 F. for several days. The roentgen examination on Feberuary 25 again

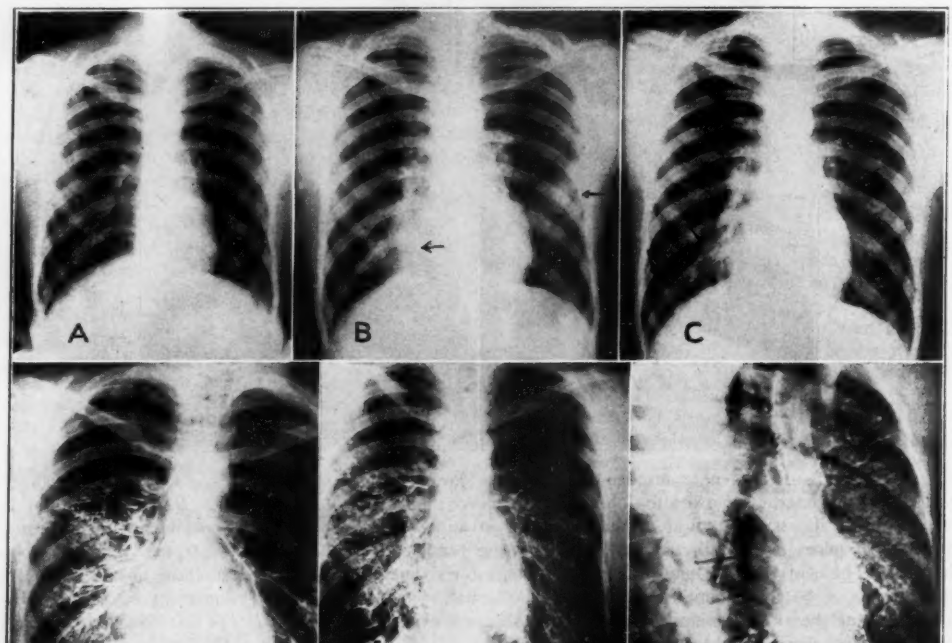

Fig. 7 (case 3).—Roentgenograms demonstrating the development of bronchiectasis in a case of atypical pneumonia. *A*, healthy chest at the time of induction into the Army. *B*, multiple foci of pneumonic involvement. *C*, clearing of the pneumonia in the left pulmonary field but persistence over a period of several months at the right cardiophrenic angle, with some evidence of atelectasis at this site. *D*, *E* and *F*, serial bronchograms over a period of four months, demonstrating no change in the degree of bronchiectasis of the lower lobe of the right lung.

Case 2.—This patient was a 21 year old white man. The past history was noncontributory except that during early childhood he had had measles, mumps chickenpox, whooping cough and scarlet fever. He had had no pulmonary complaints prior to the onset of the present illness. The induction roentgenogram showed normal pulmonary conditions. About the middle of January 1943 he contracted a cold in the chest characterized by an unproductive cough, sore throat, fever and night sweats. After three weeks the temperature suddenly rose to 104.4 F. He was hospitalized on February 2, and an initial diagnosis of atypical pneumonia of the lower lobe of the left lung was made. Examination showed slightly impaired breath sounds and fine moist rales at the base of the left lung posteriorly. showed pneumonia at the base of the left lung, and the patient continued to have impaired breath sounds and rales at the base of this lung posteriorly up to the time of discharge from the hospital on March 3. He felt well generally, but about April 1 he began coughing and raising increasing amounts of greenish yellow purulent sputum. He now complained of general debility, and his weight dropped from 146 to 120 pounds (66.2 to 54.4 Kg.). On May 30 he again had a flare-up of the pulmonary symptoms characterized by dull pain in the left side of the chest, fever and a more pronounced productive cough. He was again hospitalized. The temperature remained around 100 F. for several days, and the white blood cell count was 12,600. Roentgenograms taken on June 5 again showed the

pneumonic process at the base of the left lung (fig. 6 *B*). The patient was then transferred to Percy Jones General Hospital. Bronchograms taken on August 20 showed bronchiectasis of the lower lobe of the left lung (fig. 6 *C*). Bronchoscopic and postural drainage gave the patient temporary relief from the chronic cough and sputum, but the symptoms soon recurred. Consequently, after it was determined that the patient's symptoms of bronchiectasis were not going to be relieved by conservative management, a lobectomy of the lower lobe of the left lung was performed on November 19. The pathologic sections of the resected pulmonary tissue revealed severe chronic inflammation of the bronchi and peribronchial tissues. There were irregular, wide, branching dilatations of the bronchial lumens and formation of numerous polypoid projections of inflamed mucosa extending into them. More deeply there was complete destruction of the muscularis and replacement by fibrous scar tissue infiltrated with lymphocytes, plasma cells, histiocytes and some eosinophils. The peribronchial alveoli were atelectatic, and their septums were moderately infiltrated in the same manner as the bronchi.

CASE 3.—This patient was a 22 year old white man who in February 1943 contracted a cold in the chest associated with fever, general malaise and a productive cough. The past history was entirely noncontributory except for the fact that fourteen teeth had been extracted during the preceding six months under local anesthesia. The induction roentgenogram (fig. 7 *A*) was normal. There was no evidence roentgenologically or bronchoscopically of the presence of a foreign body causing bronchial obstruction. The symptoms were not severe enough for him to seek medical attention. During the next two months he had a moderate cough and raised variable amounts of sputum. Some days there would be none. The cough was worse when he was lying down and particularly at night. The appetite became poor, and the patient lost weight. He was hospitalized on April 23, 1943. The white blood cell count on admission was 10,300. Physical examination showed rales and slightly impaired breath sounds at the base of both lungs. The temperature was elevated to around 100 F. daily for several weeks. A roentgen examination April 28 showed bilateral pneumonia (fig. 7 *B*), particularly at the right cardiophrenic angle. After several weeks the left side of the chest cleared, but varying degrees of pneumonitis and atelectasis persisted at the right cardiophrenic border for the next four months (fig. 7 *C*). After three weeks' hospitalization the cough and sputum greatly diminished. On June 14 a small hemoptysis occurred. Because of the persistent roentgen evidence of pneumonitis and the chronic productive cough the patient was transferred to Percy Jones General Hospital on August 15. Bronchograms made on August 20 showed bronchiectasis of the lower lobe of the right lung (fig. 7 *B*). The left lung showed normal bronchial markings. During the latter part of August the patient had an acute exacerbation of his bronchiectasis, characterized by a temperature of 102 F. and a pronounced increase in the cough and purulent sputum. The patient had a bronchoscopic examination at this time. A purulent exudate covered the mucosal surface of the right main stem bronchus. The mucous membrane was swollen and inflamed, particularly about the secondary orifices of the bronchus of the lower lobe of the right lung, causing partial obstruction. The mucous membrane about the orifices was thoroughly sponged with a solution of tetracaine and epinephrine hydrochloride. After bronchoscopic drainage, the sputum increased for several days and then practically disappeared. For the past four months this patient has been entirely asymptomatic. In order to determine whether the bronchiectasis might have cleared, bronchography was repeated on two occasions over a period of four months. No change in the degree of bronchiectasis was noted, as demonstrated in the bronchograms (fig. 7 *E* and *F*). This patient is probably in a dry phase of the bronchiectasis, a period during which infection and resulting sputum are at a minimum. Because of the complete absence of signs and symptoms, lobectomy has been postponed.

CASE 4.—The patient was a 19 year old white youth whose past history was entirely noncontributory. There had been no childhood diseases and no previous attacks of pneumonia. The induction roentgenograms were normal. On Feb. 8, 1943 there developed an acute nasopharyngitis and laryngitis with a temperature of 103 F. The white blood cell count was 6,700. Physical examination showed impaired breath sounds in the base of the left lung posteriorly and occasional rales. Roentgenograms were not taken until February 22, and by this time the chest was clear roentgenologically. The patient was discharged to duty on February 26, but he continued to cough and on March 3 a left pleural pain developed. He was again hospitalized, on March 7. The temperature was elevated to 100 F. for several days and then not over an occasional 99 F. for the next several months. Physical examination of the chest at this time revealed rales and a friction rub at the base of the left lung. Roentgenograms taken on March 8 showed pneumonia at the base of this lung. Subsequent roentgenograms showed a definite shift of the mediastinum to the left and a question of a triangular shadow at the left cardiophrenic angle. During this hospitalization the cough became severe and was productive of increasing amounts of purulent sputum, up to 4 to 5 ounces (120 to 150 cc.) daily. On May 17 bronchograms revealed extensive tubular bronchiectasis in the lower lobe of the left lung. The patient was then transferred to Percy Jones General Hospital. Bronchographic examination was repeated June 8 and showed no improvement in the bronchiectasis. During this period the patient's cough, sputum and general condition became progressively worse. A lobectomy was performed on the lower lobe of the left lung on July 27. The pathologic examination revealed a diffuse process involving the bronchi and alveoli. The bronchial epithelium was pseudostratified and lay on a loose stroma of edematous granulation tissue. The bronchial musculature was almost entirely destroyed. A few remaining scattered islands of cartilage were noted, but the normal architecture had been totally altered. Occasional focal deposits of lymphoid tissue were seen in the bronchial submucosa. The outer wall of these dilated bronchi lay immediately against the parenchyma. The alveolar parenchyma was considerably reduced in volume by the interstitial fibrosis and the dilated bronchi and by atelectasis which was generally severe, leading to nearby complete airlessness. The alveolar lumens in general were either greatly contracted or filled with desquamated epithelium. The interstitial process was both fibrous and lymphohistiocytic.

CASE 5.—The patient was a 21 year old white man. Except for rubella and the usual number of colds, his past history was entirely noncontributory. The induction roentgenogram was normal. On January 19, 1943, the patient contracted a cold in the head. Two weeks later he was hospitalized, with a temperature of 103 F., sore throat, a cough productive of bloody sputum and

general malaise. Unfortunately, roentgenograms were not taken during this hospitalization. After three or four days the patient was asymptomatic, and in one week he was returned to duty. The cough persisted, and pain in the lower left part of the chest developed. On April 6 he applied for Officers Candidate School. A roentgenogram taken at this time showed pneumonitis in the lower lobe of the left lung, for which he was again hospitalized. The diagnosis at this time was atypical pneumonia of the lower lobe of the left lung. Physical examination showed impaired breath sounds and rales in this area. The temperature was 101 F. and the white blood cell count 7,100. Cough and purulent sputum steadily increased, and on April 21 bronchograms revealed bronchiectasis in the left lower lobe. The patient was then transferred to Percy Jones General Hospital. A second bronchogram, made on June 7, showed no improvement in the bronchiectasis, and clinically there was no alleviation of the symptoms. A lobectomy was performed on July 1. The pathologic examination of the removed lobe revealed complete consolidation of large areas as a result of extreme inflammation of bronchi and peribronchial alveoli, together with pronounced atelectasis. The entire bronchial wall in places was destroyed and represented by merely a thick layer of inflammatory tissue composed largely of lymphocytes, plasma cells, histiocytes, polymorphonuclears and eosinophils. The bronchial epithelium was present but was abundantly infiltrated with polymorphonuclears and in many places had undergone desquamation. Within the inflamed mucosa and submucosa were innumerable newly formed dilated blood vessels. Only scattered strands of the muscularis were identified. The adjacent alveoli showed interstitial infiltration of similar type to that of the bronchi. Within the larger inflamed bronchi, the exudate was massive and filled them completely. The alveolar parenchyma between the bronchi exhibited considerable desquamation of alveolar epithelium, especially in atelectatic areas.

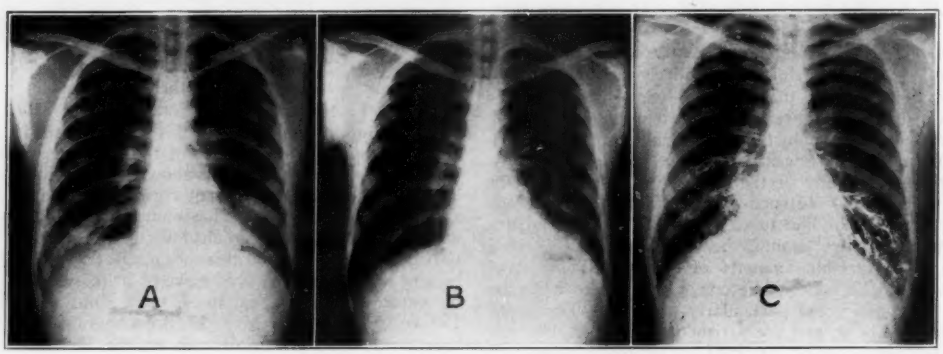

Fig. 8 (case 6).—Development of bronchiectasis in a case of atypical pneumonia. *A*, original roentgenogram at the onset of atypical pneumonia, demonstrating bilateral basilar pneumonitis. *B*, roentgenogram taken three weeks later, demonstrating clearing of the pneumonia in the right lung but persistence at the base of the left lung for the next two months. *C*, bronchogram demonstrating the development of bronchiectasis at the previous site of unresolved pneumonia.

Case 6.—This patient was a 26 year old white man who during infancy had had measles but otherwise had enjoyed excellent health. The induction roentgenogram was normal. On Jan. 10, 1943 he contracted a cold in the chest associated with cough and sputum. Five days later chills, temperature of 102 F. and general malaise occurred, for which he was hospitalized. Physical examination showed roughened breath sounds and rales at the base of both lungs but no evidence of dulness. The white blood cell count on January 18 was 11,200 and by January 25 had returned to 7,400. The sputum showed no significant organisms other than the usual bacterial flora. The first roentgenogram following the patient's admission to the hospital showed bilateral basilar bronchopneumonia (fig. 8*A*). The fever subsided after four or five days except for an occasional afternoon elevation to 99 to 99.4 F. The cough became more productive over a period of the next several months. Rales and increased dulness at the base of the left lung posteriorly were constantly observed. The right-sided basilar pneumonitis showed roentgen evidence of clearance after three weeks, but the density at the base of the left lung fluctuated as to both severity and extent of involvement for the next three to four months, as shown in figure 8*B*. Platelike areas of atelectasis were noted in the pulmonary field overlying the left part of the diaphragm that disappeared and recurred periodically during this time. Because of these observations, bronchographic examination was performed, which revealed extensive saccular bronchiectasis in the lower lobe of the left lung and the lingula (fig. 8*C*). The patient was then transferred to Percy Jones General Hospital. After a period of approximately six weeks, bronchographic examination was repeated. No improvement in the degree or severity of the bronchiectasis was noted. The symptoms remained unabated. Consequently a lobectomy and lingulectomy were done on May 30. The significant pathologic conditions of the resected pulmonary tissue were as follows: The microscopic sections revealed rather pronounced interstitial inflammation and fibrosis involving the perbronchial tissues and associated with decided dilatation of the bronchi. In addition there was considerable atelectasis, which in places was complete. The bronchoarterial sheaths showed abundant fibrous thickening and moderate cellular infiltration of plasma cells, lymphocytes and occasional eosinophils. The peribronchial and periarterial inflammation extended down to the smallest bronchus. The basic lesion here appeared to be interstitial, being confined chiefly to the peribronchial regions. Moderately ex-

tensive saccular and cylindric bronchiectasis was present.

CASE 7.—This patient was a 25 year old white man. The past history was noncontributory except for measles, whooping cough and chickenpox as a child and pneumonia at the age of 16 without sequelae. The induction roentgenograms were normal. On Feb. 8, 1943 he contracted a cold in the head and chest characterized by fever, cough, blood-tinged sputum, sore throat, nasal discharge and general malaise. Physical examination at that time revealed a nasopharyngitis, but the chest was normal. The temperature was 103 F. and the white blood cell count 4,800. On the following day on the basis of a roentgenogram of the chest a diagnosis of atypical pneumonia of the base of the left lung was made. On February 10 rales were first heard in this area. The sputum showed only the normal bacterial flora. By March 2 a new pneumonic process appeared in the upper lobe of the right lung, but there was clearing in this area after several weeks. Soon thereafter left-sided pleural effusion developed. This effusion remained sterile for approximately six weeks and then gradually became thickened. The white blood cell count at this time was 24,000. Culture now showed a hemolytic streptococcus. The empyema was drained on April 4. After drainage atelectasis of the left lung was noted, which persisted for several months. Complete healing of the empyema occurred by August. The initial productive cough subsided after several weeks but recurred around April 1, 1943. The amount of sputum increased to the extent of 2 to 4 ounces (60 to 120 cc.) daily. Because of the persistence of this productive cough, bronchograms were made on September 9. Extentive bronchiectasis of the lower lobe and lingula of the left lung was demonstrated. The patient was then transferred to Percy Jones General Hospital. Bronchographic examination on October 10 and November 18 (fig. 9) showed no alleviation of the bronchiectasis. Because of the previous empyema, lobectomy has been delayed.

Representative case histories are presented of 7 of the 17 patients seen at this hospital whose bronchiectasis, as far as can be determined, followed an attack of atypical pneumonia. Their attacks of atypical pneumonia were prolonged, and continuance of a productive cough and roentgen evidence of pulmonary pathologic conditions led to bronchographic examination and establishment of the diagnosis of bronchiectasis. Bronchographic examinations were repeated over a period of two to six months to rule out pseudobronchiectasis. Pathologic examination of the lobes resected proved the permanency and irreversibility of the condition.

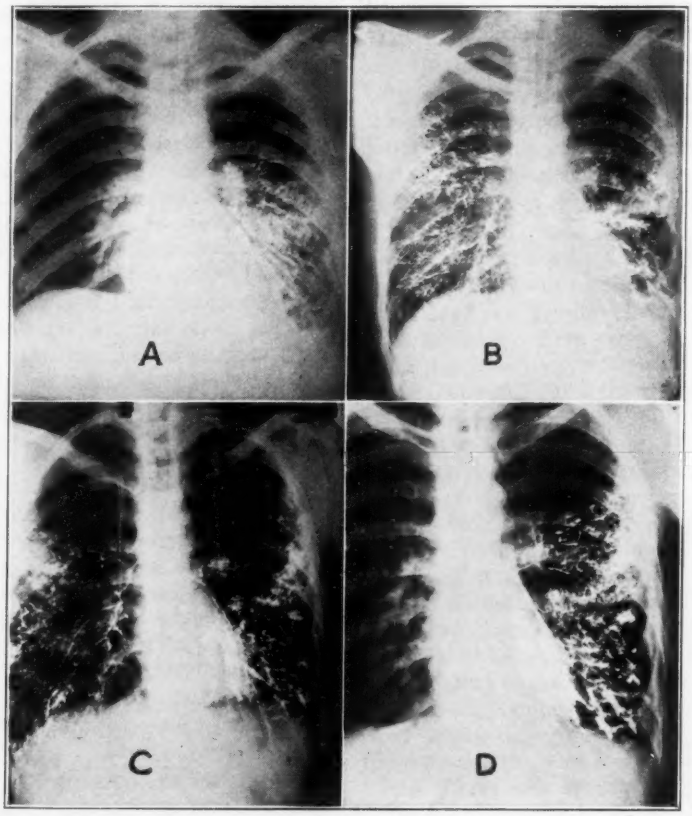

Fig. 9 (case 7).—Serial bronchograms over a period of three months, demonstrating no change in the degree of bronchiectasis during this time in a patient who previously had had atypical pneumonia.

In view of the large number of patients who have had atypical pneumonia without complications, the incidence of secondary bronchiectasis is undoubtedly small. It cannot be too strongly emphasized, however, that continued rest in bed should be insisted on until all evidences of pulmonary infection have disappeared as determined both roentgenologically and by physical examination. Van Ravenswaay stated that the sedimentation rate is a reliable index as to activity in such cases. When the atypical pneumonia runs a protracted course, and particularly when it is associated with roentgen evidence of unrelieved atelectasis, all measures should be taken to relieve the bronchial obstruction and atelectasis. Such agents would consist of expectorants, steam and menthol inhalations and postural drainage. If these fail, bronchoscopic aspiration should be done, at which time the edematous ulcerated membrane could be shrunken with epinephrine hydrochloride. If the productive cough persists, bronchiectasis should be suspected and bronchograms should be made.

Twenty-one of the entire group of 45 patients with bronchiectasis have had lobectomies, with complete relief of symptoms. There was no operative mortality.

DETERMINATION OF SEDIMENTATION RATE OF RED BLOOD CELLS

USE OF SO-CALLED CORRECTION CHARTS AND OPTIMUM LENGTH AND DIAMETER OF THE PIPET

JOHAN T. PETERS, M.D.
Visiting Professor of Medicine, Louisiana State University
NEW ORLEANS

"Correction charts" by which the observed values for the sedimentation rate are supposed to be corrected are used in many hospitals and by many practitioners in the United States. The scientific background of these correction charts is rather dubious. I began to check this scientific background after observing some instances in which in spite of a correct technic and a correct use of the correction chart the value calculated for the sedimentation rate was "negative." When I asked workers in laboratories in New York, Chicago and San Francisco about their experience in this respect, the reply was that several of them also remembered cases in which the value for the sedimentation rate was found to be "negative" after "correction" with a correction chart. Osgood [1] likewise observed such results. At my request Dr. E. Moss put at my disposal the reports of the determinations of the sedimentation rate made in the laboratory of hematology of the Charity Hospital of Louisiana in New Orleans. These were made by skilful technicians. Determinations made in the small laboratories of the wards were not included. The results of 490 determinations of the sedimentation rate were reported. Of these, not less than 28 (5.7 per cent) showed a "negative" value after correction with Wintrobe and Landsberg's chart.

It is obvious that a method which gives such absurd results in 5.7 per cent of cases must be regarded as unreliable. It is instructive, however, to try to retrace the pseudoscientific background of these correction methods. The first correction chart was constructed in 1928 by Gram,[2] whose name is also connected with the well known staining method. The leading thought of Gram was that the reading of the sedimentation rate would be more correct if he excluded the influence of a reduction of the erythrocytes below normal. To construct the chart, he altered the cell volume percentage of normal blood by addition of normal plasma in order to obtain samples with hematocrit readings between 26 and 40 volumes per cent. Two years later (1930) Rourke and Ernstene [3] tried to improve Gram's correction chart by the same sort of procedure, but by adding only so much normal plasma to the normal red blood cells that the hematocrit reading became 45. Moreover, they used heparin as an anticoagulant and warned that their chart was constructed only for heparinized blood and not for blood mixed with other anticoagulants. Five years later (1935) Wintrobe and Landsberg [4] attempted a third correction. Their chart had the advantage that it was constructed for readings of the sedimentation rate at the end of one hour. It did not require Rourke and Ernstene's time-consuming recording of degrees of settling at frequent intervals, which has, indeed, no practical value, in my opinion. Oxalated blood was diluted with increasing quantities of its own plasma. In this way six to nine dilutions were made of each sample of blood and 21 experiments were carried out, with the blood of 13 normal men and 8 normal women. The accuracy of this chart was tested with pathologic blood, obtained from 31 patients suffering from varying degrees of anemia. The sedimentation rate and the hematocrit-reading were determined. This was repeated after concentration of the blood by withdrawal of plasma. (Details may be found in the original article.) The results were compared with the readings obtained from the chart constructed as has been described. The conclusion was: "It will be seen that the correlation, although not perfect, is nevertheless quite high." This conclusion sounds too optimistic if one checks the readings. Also this method of testing the accuracy of a chart is questionable. When Wintrobe and Landsberg's tables are checked, it appears that in the 45 com-

1. Osgood, E. E.: A Textbook of Laboratory Diagnosis, ed. 3, Philadelphia, The Blakiston Company, 1940, p. 255.

2. Gram, H. C.: Acta med. Scandinav. **68**:108, 1928.

3. Rourke, M., and Ernstene, A.: J. Clin. Investigation **8**:545, 1930.

4. Wintrobe, M., and Landsberg, J.: Am. J. M. Sc. **189**:102, 1935.

parisons of patients' blood with normal blood, not less than 11 subjects, that is, about 24 per cent, had a difference in the readings of the sedimentation rate of 9 mm. or more (9 to 22 mm.). With such differences one is not justified in calling the correlations "quite high." On the contrary, such results suggest that the correction charts are not reliable.

The unreliability of this method of testing the accuracy of a chart and the unreliability of the "correction chart" itself are probably due to the fact that the influence of the plasma proteins in normal and in pathologic blood is not sufficiently appreciated. The method would be reliable if only the hematocrit reading of pathologic blood were different from that of normal blood. However, increases of the percentage of globulin and of fibrinogen in pathologic blood are the main factors of an increased sedimentation rate. Disregard of these important factors is the reason that charts constructed on such a basis are doomed to give unreliable results.

From still another angle the construction of correction charts creates doubts. They are based on the premise that anemia causes an increase in the sedimentation rate. Therefore, they are constructed by figures obtained by dilution of the red cells of a normal blood by its own plasma. However, the premise that anemia increases the sedimentation rate does not hold good for all sorts of anemia, which proves that the fundamentals on which the whole construction is built are questionable. In New Orleans, where many persons with the sickle cell trait and with sickle cell anemia are observed among the Negro population, it is a well known fact that the sedimentation rate is low if a great percentage of the red cells are sickled. Winsor and Burch [5] could confirm the findings of Bunting,[6] who stated that sickled erythrocytes often remained almost unsedimented after one hour. Winsor and Burch emphasized the influence of carbon dioxide on the shape of the red cell in sickle cell anemia and showed the diagnostic value of this influence. This, again, is probably an indirect influence of a chemical component of the plasma (HCO_3 ion) on the sedimentation rate, in this case in a direction opposite to that of the influence of increased globulin and fibrinogen. It is another warning that it is not permissible to disregard the chemical composition of the plasma in pathologic conditions, which may be quite independent of the degree of anemia. Whereas sickle cell anemia may show a low sedimentation rate, pernicious anemia, if uncomplicated, sometimes may show a normal sedimentation rate during the stage of anemia, although, as a rule, the rate is rapid. However, this possibility constitutes another argument against the fundamentals on which the correction charts are constructed.

That it is not so much the number of red cells per cubic millimeter as the radius of the red cell aggregates which determines the velocity of the sedimentation rate was pointed out by Fahraeus, the originator of the determination of the sedimentation rate. But this radius of the red cell aggregates depends on properties of the blood plasma. This can be demonstrated clearly by the following test: If erythrocytes from blood with a high sedimentation rate are suspended in plasma from a person with a low sedimentation rate, they settle at a lower rate. For this test one can use the erythrocytes of a pregnant woman and the plasma of a newborn infant.

Rourke and Ernstene tried to defend the construction of their correction chart with an appeal to the mathematician Cunningham.[7] Stoke's law about falling objects was investigated by Cunningham in 1909. He stated that the velocity of a falling object decreases in the presence of other falling objects. However, in reading Cunningham's original article one finds no support for the construction of a correction chart. Only this may be concluded from Cunningham's investigations: that the increased sedimentation rate of an aggregate of red cells would be still higher if one could exclude the influence of adjacent aggregates of red cells.

As far as the optimum length and diameter of the pipets are concerned, greatly varying conceptions are defended. A sad consequence of these controversies is that the results of several investigators cannot be compared accurately. I tried to find a solution for this problem by comparing the results obtained with pipets of varying lengths and tube diameters in combination with different kinds and varying dilutions of anticoagulants. The final decision was that longer pipets are preferable to the short ones now in vogue. This choice was made for three reasons: First, with a pathologically increasing sedimentation rate the plasma column is correspondingly much larger in the longer tubes, and thus pathologic results may be observed with more certainty. This is often of great value in dubious cases and especially in following the course of an individual case. Second, when the longer pipet, to be described here, is employed, it is possible to take advantage of the mass of statistics already compiled for the use of the

5. Winsor, T., and Burch, G.: Personal communication to the author.

6. Bunting, H.: Am. J. M. Sc. **198**:191, 1939.

7. Cunningham, E.: Proc. Roy. Soc., London, s.B **83**:357, 1909.

Westergren pipet, as will be demonstrated later. Third, in cases with a very high sedimentation rate it is often impossible to measure the rate when a short pipet is used. In such instances the opportunity for comparing results of successive determinations, often important in understanding the course of the disease, is completely lost.

To the advantage of sufficient length, I tried to add in the same pipet another advantage, a diameter which would permit the use of both venous and capillary blood. This is in contrast with Westergren's pipet, the diameter of which (2.5 mm.) does not permit the use of capillary blood. The advantages of the possibility of using capillary blood for determination of the sedimentation rate are important and often insufficiently appreciated in the literature.

In a previous paper [8] I pointed out the well known fact that in a small, but not negligible, number of patients venipuncture is not practicable. Osgood [9] discussed this objection as follows: "This [objection] is valid and the older methods should be used on certain children and obese patients with small veins." However, in the case of the measurements of the sedimentation rate, suitable older methods of venipuncture do not exist. If venipuncture of the basilic or cephalic vein at the elbow of obese patients is impracticable, other veins, such as those at the ankle, are often also unfit for venipuncture. If the difficulty arises in children, blood may be obtained from the superior longitudinal sinus before the closing of the anterior fontanel or from the jugular vein. However, many physicians dislike taking the risk of puncture of veins in the neighborhood of the brain or of important cervical blood vessels and nerves. For these reasons determination of the sedimentation rate is not infrequently omitted in cases in which this procedure would have been of great value and could have been successfully carried out with a pipet suitable for the use of capillary blood. All the pipets commonly used at this time in the United States for the determination of the sedimentation rate, are, according to their construction and directions for use, designed for venous blood. It seemed desirable, therefore, to try to perfect a pipet suitable for the use of both venous and capillary blood. The choice of the diameter of this new pipet was limited by several factors. A diameter of less than 1 mm. could not be used because of the effect of a too strong capillary attraction (Burger [10]). On the other hand, a diameter of more than 1.2 mm. could not be used in a pipet adaptable for both capillary and venous blood because of the difficulty in retaining enough capillary blood to fill the tube. Moreover, it was important to choose a diameter with which, other things being equal, results would approximate those obtained with the Westergren pipet, the diameter of which is 2.5 mm. For this purpose readings of the sedimentation rate of 30 patients made with pipets having diameters of 1.2 and 2.5 mm. respectively were compared.

Results Obtained with 2.5 Mm. (Westergren) and with 1.2 Mm. Pipet

Case	Pipet 2.5 Mm. in Diameter	Pipet 1.2 Mm. in Diameter	Case	Pipet 2.5 Mm. in Diameter	Pipet 1.2 Mm. in Diameter
1.....	7	8	16.....	14	14
2.....	5	5	17.....	13	13
3.....	5	5	18.....	5	5
4.....	4	4	19.....	6	6
5.....	20	23	20.....	8	9
6.....	9	10	21.....	3	2
7.....	8	7	22.....	4	5
8.....	20	17	23.....	3	3
9.....	16	13	24.....	14	15
10.....	9	11	25.....	11	11
11.....	5	5	26.....	9	9
12.....	10	11	27.....	2	2
13.....	2	2	28.....	20	21
14.....	16	16	29.....	2	2
15.....	5	5	30.....	20	20

The accompanying table shows that differences in results obtained with the two types of pipets are so small that the limits of normal as accepted for the Westergren pipet (2.5 mm. in diameter) are undoubtedly also valid for the pipet of 1.2 mm. diameter. Also for pathologic values the results are practically the same. As a result of these investigations a new pipet was made with a length of 30 cm. and a diameter of 1.2 mm. It fits in the Westergren racks. It is also used for the preparation of a 4:1 dilution of the blood with a 3.8 per cent sodium citrate solution. It is filled either with venous blood by suction or with finger tip blood by capillary action. The plasma column is measured with a millimeter ruler. It has only four marks. More divisions were found to be superfluous.

It would facilitate the comparison of the values for the sedimentation rate obtained with different pipets if there were one generally accepted set of standard readings. Every one who wished to continue to use his favorite pipet could standardize his model with the standard readings. I spoke with many teachers and

8. Peters, J. T.: Estimation of the Renal Function, with Aid of Iodosecretory Index and New Ureosecretory Index, Arch. Int. Med. **67**:345 (Feb.) 1941.

9. Osgood,[1] p. 461.

10. Burger, H.: Arch. néerl. de physiol. **15**:565, 1930.

practitioners who complained seriously that at the present time accurate comparisons between results obtained with different pipets are not possible because of the varying "normal" values for different pipets. It is probable that the "Westergren normal" values will be chosen for this purpose, e. g., by an international medical section of a postwar league of nations, because the Westergren pipet is by far the most commonly used throughout the world. With this pipet the largest number of values for the sedimentation rate has been collected for nearly every disease. Other pipets, each of which may have important advantages as well as disadvantages, have only local adherents. If all were standardized as just mentioned, it would be easy to decide which are the best ones. As far as the "Westergren normal values" are concerned, there is only discord among the investigators for certain age groups, namely for the age periods below 3½ and above 65 years. It will be the task of a "standardization commission" to check these claims. For the time being, it seems advisable to admit two exceptions. The "Westergren normal values" may then be summed up as follows: The normal sedimentation rate, that is, the distance in millimeters which the red cell column falls in one hour, is 1 to 10 mm. for men and 3 to 15 mm. for women. Excepted from this rule are values for subjects in the age groups between 1 month and 3½ years and above 65 years, which may reach 20 mm.

CONCLUSIONS

The only safe and sound solution of the problem of "correction" of values for the sedimentation rate is to discard all correction charts and to evaluate the observed sedimentation rate by comparison with the clinical picture, since one knows from a large body of statistics how the sedimentation rate is usually affected in different diseases. Recording of degrees of sedimentation at frequent intervals is only time consuming and gives no more information than a reading at the end of one hour. Determinations of the sedimentation rate need no longer be omitted if venipuncture is not practicable, since a pipet can be made which is suitable for both venous and capillary blood. A long pipet is far preferable to a short one. Normal and pathologic values of the sedimentation rate are practically the same whether obtained with the Westergren pipet, which is 2.5 mm. in diameter, or with a long pipet 1.2 mm. in diameter, which permits the use of either venous or capillary blood. Thus one may profit from statistics compiled from millions of readings made with the Westergren pipet.

ADENOMA OF THE ISLETS OF LANGERHANS WITH HYPOGLYCEMIA

REPORT OF TWO CASES

HARRY WALKER, M.D.
Associate Professor of Medicine
AND
WILLIAM P. BOGER, M.D.
BLUEFIELD, W. VA.

Hyperinsulinism is a broad general subject, touching on the fields of endocrinology, carbohydrate metabolism and neuropsychiatry. Furthermore, this condition presents itself in all degrees of intensity. Functional hyperinsulinism with mild hypoglycemic symptoms arising between meals or following mild exercise is common, but functioning tumors of the pancreatic islet tissue are uncommon, and even less common are growths which have been successfully removed at operation. These small adenomas of the islets of Langerhans produce recurrent severe hypoglycemic reactions, which at first yield to progressive increases of the intake of carbohydrates, but are finally cured only by the surgical removal of the adenoma. The present is a report of 2 cases of adenoma of the islets of Langerhans in which the tumors were removed surgically, with successful control after operation.

REPORT OF CASES

CASE 1. — *History.* — The patient, a single white woman 24 years of age, was born and reared in North Carolina. She spent a normal childhood and had no severe illnesses. She did creditable school work, was graduated from high school and took one year of postgraduate secretarial work. It may be worthy of note that she never obtained "steady employment." Socially she was well adjusted, but she was regarded as something of a "tomboy" and repeatedly stated that she wished "she had been born a boy." There were no abnormal trends in her behavior on this score. The family history was noncontributory.

With this ordinary history, the patient had her first "attack" on June 15, 1940. On this day the girl slept later than usual and was roused with difficulty. On being awakened forcibly she seemed "drowsy" and "acted peculiarly." At the table she smiled foolishly and fell asleep over her breakfast. Next day the patient was well, and she behaved normally until the next similar attack. There were five such spells, each characterized by "sleepiness." The patient would retire and not awaken spontaneously in the morning: Shaking was always necessary. The longest period of "sleep" was twenty hours.

In the intervals between attacks the girl "cried easily" and "was not herself," but subjectively she complained of nothing until the most recent attack, when "double vision" bothered her. During this attack incontinence was noted. This was the only attack which occurred in the daytime. Several observers failed to note any convulsions, twitchings or abnormal motor phenomena, and "sleep" was said to be normal.

The local physician referred the girl to a university hospital for study. Examination on July 11, 1940 failed to reveal anything significant. The case was turned over to the department of psychiatry, and all efforts were directed toward discovering a cause of "narcolepsy." The examiner could reach no definite conclusion and discharged the patient after prescribing 10 mg. of amphetamine sulfate twice a day. No improvement was noted.

Clinical Course.—On September 11 the patient was referred to the Medical College of Virginia Hospital with the diagnosis of "brain tumor." At examination speech was thick and hesitant, the sensorium was clouded and there was disorientation in several spheres, but there was nothing to suggest a localized neurologic lesion. A psychiatric consultant did not establish a diagnosis.

The following day the patient lapsed into coma and could not be aroused by powerful stimuli. A lumbar puncture was done, and normal changes in pressure of the spinal fluid were found. The fluid contained 2 cells per cubic millimeter and 35 mg. of protein per hundred cubic centimeters; the colloidal gold curve was normal. A determination of the sugar in the spinal fluid was not done. The concentration of bromides in the blood was 35 mg. per hundred cubic centimeters, of nonprotein nitrogen 25 mg. and of sugar 41 mg. per hundred cubic centimeters. The blood count was normal in every respect. The Wassermann reaction was negative.

On September 13 the patient had a convulsive seizure, tonic in character, which involved all the extremities and lasted about a minute; during the seizure tongue biting and incontinence were noted. Stereoscopic roentgenograms of the skull showed a normal sella turcica, and there were no evidences of increased intracranial pressure or of displacement of any structure. Because of the low blood sugar content (41 mg. per hundred cubic centimeters), feedings were given every two hours. Some improvement was noted, but there seemed to be no correlation between the symptoms and the intake of food.

On September 16 the fasting blood sugar level was 76 mg. per hundred cubic centimeters, the total intake of carbohydrate being in excess of 300 Gm. per twenty-four hours.

On September 17 the dextrose tolerance test (100 Gm. of dextrose administered orally) gave the following readings: during fasting, 70 mg. per hundred cubic

From the Department of Medicine, Medical College of Virginia.

centimeters; one hour, 200 mg.; two hours, 135 mg.; three hours, 91 mg.; four hours, 74 mg.; five hours, 52 mg.

On September 23 the girl was crying and restless and refused her food. She was given 1,500 cc. of 5 per cent dextrose solution intravenously. Her behavior became more normal after this infusion.

On September 24 ventriculograms were made; no abnormality was found.

On September 26 the fasting level of blood sugar was 36 mg. per hundred cubic centimeters, in spite of the fact that at 9 o'clock the preceding night an infusion of 1,500 cc. of 5 per cent dextrose solution had been given. An infusion of 2,000 cc. of 10 per cent dextrose solution was given through the day, but the patient was not normal in her behavior.

On September 27 a maniacal outburst required that the girl be placed in a restraining sheet, and 6 grains (0.39 Gm.) of sodium amytal was used for sedation. A stomach tube was employed, and 50 Gm. of dextrose was given every two hours throughout the day and night.

On September 30 the history of the case was reviewed. The patient's mother stated that the girl had never complained of hunger or made special efforts to obtain food between meals. At this time the patient was receiving in the hospital 600 Gm. of dextrose a day, and still the level of sugar in the blood was only 50 mg. per hundred cubic centimeters two hours after a feeding of 50 Gm. of dextrose. Surgical exploration of the pancreas was clearly indicated.

Surgical Procedure.—On October 1 an infusion of 1,500 cc. of 5 per cent dextrose in isotonic solution of sodium chloride was given immediately preoperatively; a similar infusion was given during the operation.

With the patient under general anesthesia, the abdomen was entered through a midline incision extending from the xiphoid to the umbilicus. An opening was then made in the mesocolon, and the pancreas was exposed. The body and the tail of the pancreas were carefully examined, but no abnormality was found. Palpation of the head of the pancreas revealed a small, firm nodule on the lower border of the head, in contact with the upper border of the third portion of the duodenum; this was regarded as a lymph node. The head of the pancreas was reflected by dividing the mesocolon on the right side and retracting the colon to the left. By this exposure of the posterior aspect of the head of the pancreas palpation was facilitated, and a small, firm nodule was felt within the pancreatic tissue. Several rather large vessels were found to supply this nodule; they were suitably ligated, and the nodule (a little over 1 cm. in diameter) was excised. The bed of the nodule was closed with interrupted sutures of fine silk. The opening of the mesocolon was similarly closed. Palpation of the kidneys and of the adrenals revealed no pathologic conditions. The abdomen was closed without drainage. (This operation was performed by Dr. I. A. Bigger.)

Pathologic Report.—A microscopic section of the nodule revealed a central portion composed almost entirely of collagenous connective tissue, a few cells which appeared to be fibroblasts and in the periphery numerous rather large islets which seemed larger than normal and which were not situated within the usual acinar pancreatic epithelium. These islets had also an irregular arrangement, but the epithelial cells composing them were regular and in no way differed from those found in a normal pancreas. In some of the islets, however, there was moderate collagenous connective tissue, which appeared to be similar to the tissue making up the greater part of the central portion of the nodule. Surrounding these structures was a small portion of what seemed to be normal pancreatic tissue. What few blood vessels and other structures were present appeared to be normal. There was no evidence of specific inflammatory change. The condition was diagnosed as benign adenoma of the islets of Langerhans of the pancreas with marked central fibrosis.

Course After Operation.—Six hours after the operation the blood sugar was found to be 113 mg. per hundred cubic centimeters; no dextrose had been given after the operation.

On October 3 the patient was mentally alert and more nearly normal than at any previous time during her stay in the hospital.

During the night of October 4 the patient fell out of bed, apparently because of a nightmare; there was no mental confusion.

On October 7 the patient was doing well clinically, but her bad humor and conduct were reminiscent of her preoperative behavior.

On October 13, the twelfth postoperative day, the girl left the hospital.

On the second, fourth, sixth and eight postoperative days the fasting levels of sugar in the blood were, respectively, 130, 92, 88 and 85 mg. per hundred cubic centimeters.

Subsequent checks on this patient reveal that at the time of writing, two years after the operation, she is in excellent health.

Comment on Case 1.—The total duration of symptoms was three and a half months, and until the last three weeks the chief complaint was the "sleepiness" on five occasions. Symptoms were so mild that the diagnosis of "neurosis" had been entertained. It is of interest that this patient had never complained of hunger and had never relied on ingestion of food to relieve her symptoms; indeed, the taking of more than 600 Gm. of dextrose a day failed to control her symptoms while she was being observed in the hospital.

This case gives rise to certain interesting speculations. If the patient's first attack of "sleepiness" was due to overproduction of insulin by the adenoma—an assumption which seems justified, since her symptoms were promptly relieved by the removal of the adenoma—why were the symptoms not progressive from the time of their onset? An adenoma of a pancreatic islet is a new growth, and the cells which compose the adenoma are elaborating an active hormone, as is substantiated by the isolation of insulin or an insulin-like substance from the adenoma. Unfortunately we have no positive data as to the rate of growth of an adenoma, and we have no assurance that its size increases at a uniform rate. If the increase in size is constant it might be expected that the amount of insulin

produced would likewise progressively increase and that symptoms would be aggravated accordingly. In this case, however, while from the long range point of view symptoms were progressive in severity, the rate of evolution of symptoms in the last three weeks was out of proportion to that in the previous three months. Indeed, the isolated episodes of "sleepiness," with comparative freedom from symptoms between, speak for an inconstant, erratic overproduction of insulin. This observation would seem to harmonize with dysinsulinism, or disorderly production of insulin, as opposed to hyperinsulinism, or overproduction of insulin. We shall return to this point in the general discussion.

This case is witness to the truth that "hyperinsulinism takes another syndrome from the wastebasket of neuroses.[1] Hyperinsulinism should be considered, if only to be ruled out, as a possibility in every neuropsychiatric case.

CASE 2.—*History.*—The patient was a white woman, 67 years of age and widowed. She prided herself on her good health, had never suffered a serious illness and had passed through the climateric at the age of 50 without incident. Five years before (1938) the complaint of "double vision" had taken her to a physician. A low level of blood sugar having been found on several occasions, she was advised to take 2 ounces (60 Gm.) of dextrin every two hours. As a result of this program of increased intake of carbohydrate 30 pounds (14 Kg.) was gained and the diplopia was relieved. In 1940 the patient began to have "attacks," which consisted in "failing to awaken in the morning" or in being overcome by sleepiness. This sleepiness was so insidious that the patient herself credited it only to her good fortune that she had been "found in time," for she was frequently unable to do anything to help herself. Nausea accompanying the attacks made the taking of food difficult when food was offered as a restorative.

Clinical Course.—On Oct. 19, 1942 this woman was admitted to the Medical College of Virginia Hospital. She was so obese that physical examination was of limited value. The patient was cooperative and was in no distress; she was slow of speech and had a coarse tremor of the hands and a slight weakness of the right side of the face. The optic fundi presented marked angiolar sclerosis and tortuosity, with prominent arteriovenous nicking; there were no exudates or hemorrhages. The blood pressure was 190 systolic and 130 diastolic in both arms; the heart sounds were poorly heard; the lungs were clear; no masses or enlarged viscera were felt in the abdomen.

On the afternoon of admission an attack was observed; the patient appeared dazed, looked vacantly into space, was unable to respond intelligibly, was disoriented and perspired profusely with a cold, beaded perspiration standing out on the forehead and the extremities; the weakness of the right side of the face was more pronounced, the breathing was stertorous and the pulse full and bounding. There was no drop in the blood pressure. The patient had difficulty in swallowing, but shortly after being given 2 ounces (60 Gm.) of dextrin orally she began to recover. She was able to talk clearly fifteen minutes later. There was complete amnesia with respect to the attack and for at least fifteen minutes prior to the appearance of the observable symptoms.

A diet including 300 Gm. of carbohydrate and additional feedings of dextrin was prescribed; nevertheless there was an attack almost daily in the late afternoon or early evening; indeed, the attacks occurred so regularly that the nursing staff was able to recognize the patient's vacant stare and perspiring in advance of a "fully developed insulin shock" and to anticipate the attack by giving her dextrin or sweetened fluids. Determinations of the blood sugar at the onset of symptoms repeatedly revealed it to be low: 22, 40, 36 and 28 mg. per hundred cubic centimeters.

Surgical Procedure.—The patient's hypertension, cardiac enlargement, age and myocardial damage as demonstrated by electrocardiographic evidence made her a poor surgical risk, but the risk was accepted. An infusion of dextrose was given preoperatively and a second during the operation. With the patient under intercostal nerve block and intravenous pentothal sodium anesthesia, a right rectus muscle-splitting incision was made. There was a heavy layer of subcutaneous fat, and the underlying structures were extremely poor. The anterior rectus sheath, the rectus muscle and the posterior rectus sheath were exceptionally friable. There was heavy deposition of fat in the omentum and the abdominal structures. . . . The pancreas was exposed through an opening in the gastrocolic omentum. Almost immediately a firm nodule was felt at the tip of the uncinate process of the head of the pancreas. The body and the tail of the pancreas were palpated, and no other nodules were found. Exposure was difficult, and the nodule would have been more readily approached by reflection of the duodenum, but this was not feasible because of adhesions between the gallbladder and the duodenum; the cause of these adhesions could not be determined. The nodule was removed, but not without considerable hemorrhage from the rather large vessels supplying the nodule. The bed of the nodule was closed with interrupted mattress sutures. A frozen section of the nodule from the pancreas was returned by the pathologist with the notation that it was "compatible with pancreatic adenoma." A drain was placed in the lesser peritoneal cavity, but the drain was not in contact with the wound in the pancreas. The closure of the wound was unsatisfactory because of the poor quality of the tissues of the abdominal wall. The patient left the operating room in good condition. (The operation was done by Dr. I. A. Bigger.)

Pathologic Report.—The section consisted of a complete cross section of a well encapsulated nodule from the pancreas. On the external surface there was a small amount of recognizable pancreatic tissue containing both acinar tissue and a few islets. The nodule was composed of nests of uniform cells with vesicular nuclei and a moderate amount of cytoplasm and having a striking resemblance to islet cells of the pancreas. The nests of cells were separated by broad bands of hyalinized fibrous connective tissue, which made up probably

1. Evans, J. A., and McDonough, W.: Hyperinsulinism: Case Reports and Discussion, J. Iowa M. Soc. **23**:454-460, 1933.

one fourth of the area of the nodule. The diagnosis was a benign islet cell adenoma of the pancreas (nesidioblastoma).

Course After Operation.—The blood sugar was 93 mg. per hundred cubic centimeters nine hours after the operation, a value higher than any obtained preoperatively. Nausea and vomiting were troublesome for several days, and drainage from the wound was considerable, this having been anticipated because of the poor closure of the wound. There were no further attacks; the patient felt remarkably well, and was discharged to a convalescent home on Nov. 23, 1942.

At the nursing home the patient did well for a few days, but since she then began to vomit five to ten times per day, it was thought wise to readmit her to the hospital. Examination revealed a 30 pound (14 Kg.) loss in weight and a clean operative wound with a small sinus, from which drained a small quantity of watery discharge. There was no digestion of skin

Fig. 1.—Tumor of the islets of Langerhans removed from the patient in case 2, showing fringe of pancreatic tissue around the well defined capsule. The tumor weighed 1.032 Gm. and measured 1 by 1.2 by 0.9 cm.

about the mouth of the sinus, and the blood pressure was 204 systolic and 140 diastolic.

A roentgen study of the gastrointestinal tract showed there was no deformity of the stomach or of the duodenum, but unusual looping of the second and third portions of the duodenum, with slight pressure on the greater curvature of the stomach compatible with enlargement of the head of the pancreas and pressure of the head of the pancreas on the pylorus and the duodenum.

The serum amylase was found to be 36 units (normal 20 units). On the basis of this finding and of the results of a roentgen examination it was suggested that the patient's nausea and vomiting were due to pancreatitis set up by the operation; so no active measures were taken by way of treatment.

Convalescence was uneventful, and the patient was discharged Dec. 23, 1942.

The only laboratory work of significance in this case was that concerned with the metabolism of carbohydrates. This information is presented graphically (fig. 4).

Comment on Case 2.—This patient is one of the oldest patients on record who have recovered after the removal of an adenoma of the islets of Langerhans. The recovery is all the more notable because of the factors which made her a poor risk.

The studies done on this patient were not numerous, and it may be unwise to postulate anything on the basis of so few data, but certain points brought out by the tests are of interest. The dextrose tolerance test was done after what is accepted as suitable preparation, i. e., administration of 300 Gm. of carbohydrate daily for three days prior to the test. The half-hour rise after the ingestion of 100 Gm. of dextrose was distinctly of a diabetic type, and similarly the one, two and three hour levels of sugar in the blood may be called diabetic; yet the fasting level and the four hour level proclaim this curve to have been obtained from a patient with hypoglycemia. From this curve it may be inferred that there was marked intolerance for dextrose, but that insulogenesis was stimulated and that in four hours the fasting level was restored. It is of interest that the patient felt well at the termination of this test. This curve offers an interesting comparison with the one which resulted when the curve of tolerance for dextrose was modified by intravenous injection of 3.4 units of insulin. The second curve shows curtailment of the rise in the amount of sugar in the blood. From this curve it would appear that on practical grounds there is merit in Johns's recommendation that a small dose of insulin should precede feedings of a patient with hyperinsulinism in order to reduce the stimulus to insulogenesis. Since such a small amount of insulin modified the dextrose tolerance curve so markedly, the unmodified curve would seem to indicate that insignificant quantities of insulin were circulating in the blood at the time the dextrose tolerance test was begun and that only after stimulation by the ingested carbohydrate was enough insulin produced to lower the level of sugar in the blood to hypoglycemic levels. If this assumption is correct, it would seem that the adenoma of the pancreas is not constantly producing insulin in quantity and that the adenoma is, at least in some measure, controlled by the normal mechanisms which stimulate and inhibit the production of insulin. We shall return to this last surmise in the general discussion.

After the test for tolerance of dextrose and insulin combined, 0.7 cc. of a 1 : 1,000 solution of epinephrine hydrochloride was given subcutaneously, and no rise in the level of sugar in the blood was obtained. Either epinephrine in this quantity was not capable of raising the level of sugar in the blood above the level already

existent, or this quantity of epinephrine could not offset the action of as little as 3.4 units of insulin given two hours previously. It might seem, then, that the observation in various cases of hyperinsulinism that epinephrine has an inconstant effect on the level of sugar in the blood may be explained by the different quantities of insulin acting at the times when epinephrine was administered.

The results of dextrose tolerance tests done postoperatively are presented in figure 3, together with the results of a preoperative test. The contrast is striking. There is little to be said concerning the curve done on Nov. 20, 1942, but the curve of December 22 is unequivocally of diabetic type. It would seem, then, that the patient was treated for an adenoma of the islet tissue, which produced hypoglycemia, and yet almost two months later she had a dextrose tolerance curve of definitely diabetic type. Transient diabetic tendencies during the first postoperative days are common, even ketonuria having been noted,[2] but such a definitely diabetic type of curve so long after operation has not been frequently reported. It is to be regretted that we lost contact with this patient and were unable to carry out further studies.

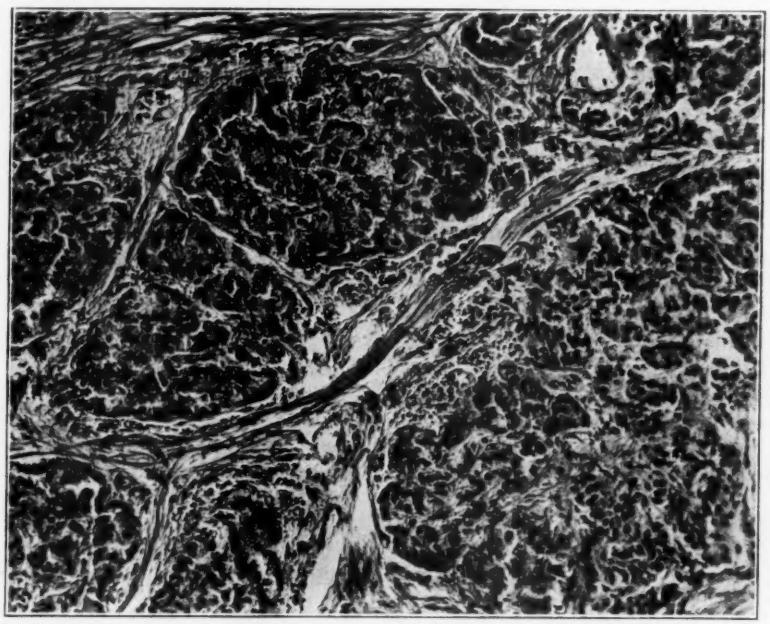

Fig. 2.—Photomicrograph of the tumor removed from the patient in case 2, showing bands of fibrous tissue. The pathologist's description appears in the text.

GENERAL COMMENT

Despite the fact that the symptoms of hyperinsulinism are those of hypoglycemia, the terms are not synonymous. Conn [2] has offered a satisfactory classification of the various types of spontaneous hypoglycemia, and it is not the province of this paper to discuss hypoglycemia generally. We are specifically interested in the adenoma of the islets of Langerhans (insuloma [3] or nesidioblastoma [4]) as a cause of hyperinsulinism and hypoglycemia.

Incidence of the Disease.—Though there are fairly frequent reports of islet tumors, the removal of an adenoma at operation with recovery by the patient is still relatively rare. Frantz [5] in 1940 reported 96 islet tumors with hypoglycemia, and Keating and Wilder [6] in 1941 raised the number to 106, but analysis of these figures reveals that only 44 were benign pancreatic adenomas successfully operated on. We

2. Conn, J. E.: The Spontaneous Hypoglycemias: Importance of Etiology in Determining Treatment, J. A. M. A. **115**:1669-1675 (Nov. 16) 1940.

3. Harris, S.: The Diagnosis of Surgical Hyperinsulinism, South. Surgeon **3**:199-210, 1934.

4. Laidlaw, G. F.: Nesidioblastoma, the Islet Tumor of the Pancreas, Am. J. Path. **14**:125-134, 1938.

5. Frantz, V. K.: Tumors of Islet Cells with Hyperinsulinism: Benign, Malignant and Questionable, Ann. Surg. **112**:161-176, 1940.

6. Keating, F. R., and Wilder, R. M.: Spontaneous Hypoglycemia: Report of Cases, South. Med. & Surg. **103**: 125-131, 1941.

have not reviewed the literature exhaustively, but we were able to find records of 10 more similar tumors.[7] These cases together with those of Keating and Wilder are presented in the accompanying table. Thus with these 2 cases of our own the number of operative cures of pancreatic adenoma is raised to 56. This condition, therefore, is still rare.

Symptoms.—The symptoms of these tumors are readily postulated as those of "insulin shock," but their multiplicity defies enumeration. Headache, weakness, dizziness, nausea, sweating, tachycardia, hypothermia, lowering of the blood pressure and diplopia are common. Neurologic signs and symptoms may be encountered alone or in any combination.[8] The frequency of a positive Babinski sign, which disappears on the relief of hypoglycemia, is worthy of comment. Hunger has been emphasized in many reports, but both of our cases illustrate the fact that it is not a universal symptom. Convulsions are common and are by many considered characteristic of the condition, but patient 1 had convulsions only after three months of symptoms, and patient 2 in five years of symptoms was never observed to have a convulsion.

The lack of correlation between the occurrence of symptoms and the level of the sugar in the blood has been noted. The explanation for this lack of correlation is not clear. At one time the patient may have symptoms with a level of sugar in the blood which at another time produces no symptoms. Persons familiar with the use of protamine zinc insulin have noted the paradox in the existence of symptoms of shock with blood sugar levels well over 100 mg. per hundred cubic centimeters. It has been suggested that it is not the level of sugar in the blood per se which produces the symptoms, but the rapidity with which the hypoglycemia has been produced. If the fall in blood sugar is precipitous, symptoms will be elicited at a higher level than if the fall is gradual. The dextrose tolerance curve in case 2 is of interest in this regard: After the ingestion of 100 Gm. of dextrose the decline to

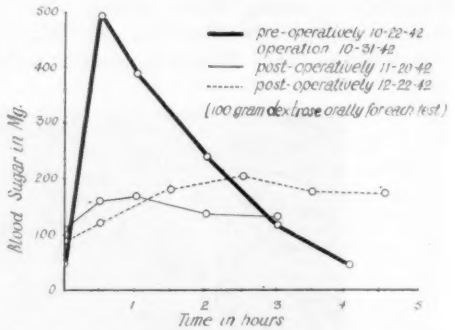

Fig. 3.—Results of the dextrose test for the patient in case 2, showing the effect on the blood sugar level of ingestion of 100 Gm. of dextrose.

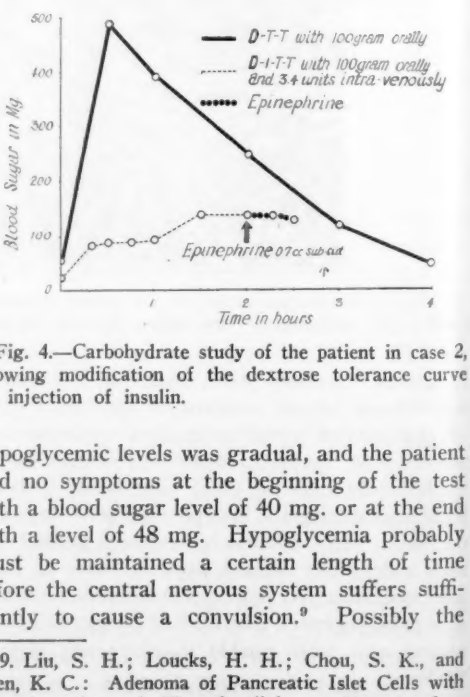
D-T-T with 100gram orally
D-T-T with 100gram orally and 34 units intra-venously
Epinephrine
Epinephrine 0.7 cc sub-cut
Blood Sugar in Mg.
Time in hours

Fig. 4.—Carbohydrate study of the patient in case 2, showing modification of the dextrose tolerance curve by injection of insulin.

hypoglycemic levels was gradual, and the patient had no symptoms at the beginning of the test with a blood sugar level of 40 mg. or at the end with a level of 48 mg. Hypoglycemia probably must be maintained a certain length of time before the central nervous system suffers sufficiently to cause a convulsion.[9] Possibly the

7. (*a*) Meyer, K. A.; Amtman, L., and Perlman, L.: Islet Tumors of the Pancreas: Report of a Case, J. A. M. A. **117**:16-20 (July 5) 1941. (*b*) Vayo, P. G., and Bodon, G. R.: Adenoma of Langerhans' Islet of the Pancreas, Am. J. Surg. **54**:744-746, 1941. (*c*) Magner, W.: Hyperinsulinism: A Report of Two Cases, Canad. M. A. J. **45**:49-52, 1941. (*d*) Greenlee, D. P.: Pancreatic Islet Tumors with Hypoglycemia, Pennsylvania M. J. **43**:809-812, 1940. (*e*) Burtness, H. I.; Koehler, A. E., and Saint, J. H.: Hyperinsulinism Due to Adenoma of the Islets of Langerhans: Case Report with Metabolic Studies Before and After Removal of Tumor, Ann. Int. Med. **14**:1915-1932, 1941. (*f*) Rudd, T. N., and Walton, J.: A Case of Islet Adenoma, Brit. J. Surg. **29**:266-270, 1941. (*g*) Holman, E.; Wood, D. A., and Stockton, A. B.: Unusual Cases of Hyperinsulinism and Hypoglycemia, Arch. Surg. **47**:165-177 (Aug.) 1943. (*h*) Erb, W. H.; Dillon, E. S., and Ferguson, L. K.: Symposium of New Trends in Surgery: Islet Cell Adenoma, S. Clin. North America **22**:1663-1675, 1942. (*i*) Adenoma of Pancreatic Islet Cells, Cabot Case 27151, New England J. Med. **224**:659-660, 1941. (*j*) Conn.[2]

8. Sigwald, J.: L'hypoglycémie, Paris, Gaston Doin, 1932. Wilder, J.: Klinik und Therapie der Zuckermangelkrankheit, Vienna, Verlag für Medizin, Weidmann & Co., 1936.

9. Liu, S. H.; Loucks, H. H.; Chou, S. K., and Chen, K. C.: Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism: Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, J. Clin. Investigation **15**:249-260, 1936.

dextrose tolerance curve explains why patient 2 never had convulsions. Yet this suggestion is not wholly satisfactory, for cases are reported in which patients had blood sugar levels of 30 mg. or less for a number of hours without any symptoms at all.[10] The relationship between hypoglycemia and symptoms is still in need of clarification, especially since about 20 mg. per hundred cubic centimeters of the blood sugar according to the Folin-Wu analysis is made up of reducible substance other than dextrose.

subject to extensive fibrosis, hyaline degeneration and calcification.[4] These observations have been made so frequently that no further comment is needed. Most adenomas are completely encapsulated, but even those tumors whose capsules are incomplete microscopically and show invasion by blood vessels behave like benign neoplasms. Frantz [5] cited 15 cases of adenomas suspected of being malignant and removed at operation, some patients having survived five and ten years without recurrence of symptoms.

Benign Adenomas of the Islets of Langerhans Removed at Operation with Recovery of the Patients

Reference (See Text)	Age	Sex	Duration of Symptoms	Type of Symptoms	Lowest Blood Sugar, Mg. per 100 Cc.	Tumor		Insulin Extracted	Comments
						Site	Size		
7a	41	F	18 mo.	"Spells" "unconsciousness"	"Too low to read"	Body	2 by 1.8 by 1.5 cm.	No	.....
7b	60	F	"Several mo."	"Stupor"	31 mg.	Junction body and tail	4 by 4.5 by 2 cm.	No	Associated Paget's disease
7c Case 1	52	M	8 yr.	"Unconscious once daily for 5 yr."	35 mg.	Junction head and body	2 cm. in diameter	No	.....
6 Case 1	56	F	?	"Unconsciousness relieved by food"	38 mg.	Tail	"Small"	No	Transient postoperative diabetes; retention cyst
Case 2 6	55	F	2½ yr.	"Convulsions and unconsciqusness"	38 mg.	Head	?	No	Diabetes for 48 hr. postoperatively
Case 3 6	33	M	18 mo.	"Weakness, convulsions, unconsciousness"	32 mg.	Body	"Small"	No	Normal electroencephalogram
Case 4 6	44	F	15 yr.	"Unconscious spells for 4 yr."	40 mg.	Body	"Small"	No	Pancreatic fistula
Case 1 7d	56	F	2½ yr.	"Unconsciousness"	"Too low to read"	Junction tail and body	1.5 cm.	Yes	Thyrotoxicosis and hypoglycemia
Case 2 7d	61	F	6 mo.	"Fainting, dizziness, convulsions"	29 mg.	Tail	1 cm. in diameter	Yes	.....
7e	43	F	7 yr.	"Weakness, diplopia, personality change"	34 mg.	Junction body and tail	1.5 cm. (1.304 Gm.)	No	Transitory diabetes mellitus
7f	29	M	8 mo.	"Stupor, nervousness"	48 mg.	Ligaments between pancreas and spleen	1.3 cm.	No	Extrapancreatic location of adenoma
7g	?	F	6 mo.	"Irritable, disoriented, queer behavior"	37 mg.	Tail and gastrosplenic ligament	0.7 cm. and 2.0 cm.	No	Extrapancreatic adenoma; 2 tumors
7h	38	M	18 mo.	"Sweating, clonic jerks of arm"	26 mg.	Head	2 by 1 by 1 cm.	No	Relieved for 6 weeks by diet and cortical hormone
7i	29	F	3 yr.	"Always hungry, dizzy; coma"	26 mg.	?	?	No	.....
2	59	F	10 yr.	"Hunger, dazed spells, jerks of arm"	24 mg.	Tail	From 0.5 to 1.5 cm.	No	Four separate adenomas

But regardless of the clinical manifestations, which are so confusing that hyperinsulinism frequently masquerades as neurosis, brain tumor, epilepsy, narcolepsy and alcoholism, the diagnosis rests on the demonstration of a blood sugar value below 50 mg. per hundred cubic centimeters and on symptoms which are relieved by the administration of carbohydrates. These conditions are readily met by a case of adenoma of the pancreatic islets.

Pathologic Changes.—Pathologically, islet tumors are gigantic islets and produce lesions of the islets on a grand scale, for nontumoral islets are

Nevertheless frank carcinoma with metastases has been frequent enough [11] to compel us to regard these adenomas as neoplasms.

10. Murphy, R. G.; Dustin, C. C., and Bowman, R. O.: Hyperinsulinism Due to Adenoma of the Pancreas, J. Lab. & Clin. Med. **24**:1050-1054, 1939.

11. (*a*) Holman, Wood and Stockton.[7g] (*b*) Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**: 348-355 (July 30) 1927. (*c*) Judd, E. S.; Faust, L. S., and Dixon, R. K.: Carcinoma of the Islands of Langerhans with Metastases to the Liver Producing Hyperinsulinism: Report of a Case, West. J. Surg. **42**:555-557, 1934. (*d*) Cragg, R. W.; Power, M. H., and Lindem, M. C.: Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism, Arch. Int. Med. **60**:88-99 (July) 1937. (*e*) Joachim, H., and Banowitch, M. M.: A Case of Carcinoma of the Islands of Langerhans with Hypoglycemia, Ann. Int.

(Footnote continued on next page)

Still, certain facts indicate that these tumors of the islets are unusual in their behavior:

1. Why are the tumors so uniform in size, regardless of the length of time the patient has had symptoms? The average diameter is 0.5 to 1.5 cm.; most of the tumors are described as "about a centimeter in diameter," and one more than 2 cm. in diameter is unusual. Patient 1 had symptoms for three and one-half months and patient 2 for five years; yet the tumor in each instance was about 1 cm. in diameter.

2. The component cells of these tumors secrete an active hormone.[12] If these cells are neoplastic one would expect them to secrete regardless of the need of the body for their secretion. Why, then, are symptoms not steadily progressive once they appear? In the description of both of our cases we have pointed out that between "attacks of sleepiness" there was relative freedom from symptoms. This would seem to indicate inconstant production of excessive insulin.[7a]

3. Why are some of the tumors comparatively cellular, while others are markedly fibrotic and even calcified? The vascularity of these tumors, frequently reported, is a strong point against any argument of insufficiency of the supply of blood. The small size of the tumors makes it unlikely that they outgrow their blood supply, with resultant degeneration and fibrosis. Again, fibrosis cannot be entirely a matter of aging of the tumors, for in case 1 there was considerable fibrosis and yet symptoms had been noted for only three and one-half months. But the question can be asked whether it is accurate to consider the age of a tumor identical with the duration of symptoms. Surely these tumors do not produce symptoms the moment they exceed the size of normal pancreatic islets. What, then, is the critical size of the tumors, at which they produce symptoms?

4. Why are the tumors so frequently multiple?[13] Frantz[5] in describing 96 cases of islet tumors cites 11 in which there was more than one tumor.

These questions are raised not because we have the answers but because when one tries to answer them it becomes clear that one can best harmonize the observations that have been made by regarding islet tumors as functioning units in the endocrine system. As such they are subject to the same inhibition and stimulation as normal islets, but to a lesser degree because they are neoplasms.

Connection with the Physiology of Insulin.—The physiology of insulin is too complex to be discussed here, but certain aspects of the subject will be of service to us. Fraser and others[14] pointed out that the effect of insulin in lowering the level of sugar in the blood is opposed by the action of adrenal cortical hormones in promoting glyconeogenesis and by the glycotropic hormone of the pituitary gland. Normally these antagonists are nicely balanced, so that they compensate for each other. In a case of hyperinsulinism in which symptoms are clearcut and hypoglycemia is controlled with difficulty, it seems accurate to say that the system of checks and balances has become inoperative. But, as we have pointed out, this point is not reached at once; indeed the patient may do fairly well for years. It seems that there is an important place in our concept of hyperinsulinism for a "compensating-decompensating" phase preceding the final appearance of intractable hypoglycemia. The factor which determines the issue is that on one hand there are physiologic mechanisms, while on the other there is a neoplasm, the pancreatic adenoma. If the neo-

Med. **11**:1754-1759, 1938. (*f*) Flinn, L. B.; Beatty, G. A.; Ginsberg, M., and Memsath, F.: Carcinoma of the Islands of Langerhans with Hypoglycemia and Metastases to the Liver, J. A. M. A. **117**:283-285 (July 26) 1941. (*g*) Ballinger, J.: Hypoglycemia from Metastasizing Insular Carcinoma of Aberrant Pancreatic Tissue in the Liver, Arch. Path. **32**:277-285 (Aug.) 1941. (*h*) Bickel, G.; Mozer, J. J., and Junet, R.: Diabète avec dénutrition grave. Disparition de la glycosurie et atténuation progressive de l'hyperglycémie à la suite du développement d'un carcinome insulaire du pancréas avec métastases hépatiques massives, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:12-21, 1935.

12. (*a*) Greenlee.[7d] (*b*) Wilder, Allan, Power and Robertson.[11b] (*c*) Bickel, Mozer and Junet.[11h] (*d*) Akerberg, E.: Hyperinsulinism and Surgery, Acta chir. Scandinav. **83**:104-122, 1939. (*e*) Campbell, W. R.; Graham, R. R., and Robinson, W. L.: Islet Cell Tumors of the Pancreas, Am. J. M. Sc. **198**:445-454, 1939. (*f*) Derick, C. L.; Newton, F. C.; Schulz, R. Z.; Bowie, M. A., and Pokorny, N. A.: Spontaneous Hyperinsulinism: Report of Case of Hyperinsulinism Cured by Surgical Intervention, New England J. Med. **208**:293-298, 1933. (*g*) Graham, E. A., and Womack, N. A.; The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and Other Conditions, Surg., Gynec. & Obst. **56**:728-742, 1933. (*h*) Isaji, M.: On Islet Cell Adenoma and Islet Cell Carcinoma of the Pancreas, Frankfurt. Ztschr. f. Path. **53**:178-207, 1939. (*i*) Kerwin, A. J.: Fatal Hyperinsulinism with Cerebral Lesions Due to Pancreatic Adenoma, Am. J. M. Sc. **203**:363-370, 1942.

13. Conn.[2] Wilder, Allan, Power and Robertson.[11b] Joachim and Banowitch.[11e] Graham and Womack.[12g]

14. Fraser, R.; Albright, F., and Smith, P. H.: Carbohydrate Metabolism: The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism. J. Clin. Endocrinol. **1**:297-306, 1941.

plasm is truly carcinomatous, growth is rapid and hypoglycemia is fulminating; a few such cases have been encountered. By far the majority of the tumors, however, probably grow slowly, and by this circumstance the endocrine compensatory mechanisms are called into play, so that even if the islet adenoma continues its growth at a slow but steady pace, the body is capable of adjusting at different levels of production of insulin. We feel that such a concept harmonizes with the observed facts in cases of benign pancreatic islet tumor.

Duff [15] stated that there is no authenticated example of spontaneous cure occurring as a result of generative changes in an islet cell adenoma. Such a cure would be difficult of proof, but theoretically there is a possibility of spontaneous recovery with the proper concomitance of fortuitous events. Young [16] has demonstrated in dogs that with repeated injections of extracts of the anterior lobe of the pituitary gland he can produce permanent diabetes. Because of the lack of a potent preparation this method cannot be applied to human beings; unless there were available a preparation with selective action affecting only the overproduction of insulin there would be a distinct possibility of disturbing other members of the endocrine system. Allen [17] nevertheless suggested this therapy with Young's extract in the event of severe "insulin intoxication." Fraser and others [14] pointed out that nature furnishes an interesting experiment in that "a patient with acromegaly may be at the stage of 'compensating hyperinsulinism' or may end by having hypoinsulinism like a 'Young dog.'" In short, this last statement seems to contain the crux of the matter: From the anterior lobe of the pituitary gland may come the stimulus which determines overproduction of insulin by pancreatic islet tissues, or underproduction of insulin through overstimulation and exhaustion of islet tissues. Thus diabetes mellitus and hyperinsulinism stand in close relationship to each other through the common factor insulin, the production of which is immediately a function of the islets of Langerhans but is influenced by other members of the endocrine system.

The case of Bickel and others [11h] is of great interest, for the patient in this case received as much as 100 units of insulin daily, and as much as 240 Gm. of dextrose was excreted in the urine in a day. It was observed that the glycosuria disappeared in the course of four months, so that more dextrose was tolerated than formerly when 100 units of insulin was given daily. This patient died, and a carcinoma of the islets of Langerhans with hepatic metastases was found; insulin was isolated from the primary growth but not from the hepatic metastases.

Though such a conclusion is purely speculative, it would seem that this case indicates that perhaps there was a supreme effort made by the anterior lobe of the pituitary gland to stimulate the production of insulin in a definitely diabetic patient and that some tissues of the islets responded and gave rise to a growth, which in this case became malignant. In this case, contrary to the experience with Young dogs, the stimulated islet tissues did not become "exhausted," but overleaped the bounds of normalcy and became malignant. But following the reasoning used in the Young experiments with dogs, in an adenoma of the islets of Langerhans which is overproducing insulin the anterior lobe of the pituitary gland by compensatory overproduction of glycotropic hormone might conceivably inhibit all of the normal islets of the pancreas, producing true diabetes, which is masked by the presence of the adenoma. Surgical removal of the adenoma should result in a diabetic state. We cannot refrain from commenting that in case 2 there was a truly diabetic curve even two months after operation. The observation of transient diabetes after adenomas are removed is almost universal; it seems nearly certain that if these cases are followed up some patients will prove to have permanent diabetes.

This adventure into the field of endocrinology may contribute little of practical import at present, but it is fruitful in the matter of understanding the broader implications of hyperinsulinism and of looking forward to the therapeutic attack on this condition with endocrine products.

Treatment.—At present the treatment of adenoma of the islets is surgical removal as soon as the diagnosis is reasonably established. Dietary management by increasing the intake of carbohydrate alone finally fails to control the symptoms and may actually aggravate the disease. Diets high in protein, high in fat and moderate in carbohydrate have had some success in the management of mild hyperinsulinism of the functional sort, but not much in the handling of cases involving islet tumors. The use of insulin before meals to prevent the sharp postprandial rise in blood sugar and so lessen the stimulus to the

15. Duff, G. L., and Murray, E. G. D.: The Pathology of Islet Tumors of the Pancreas, Am. J. M. Sc. **203**:363-370, 1942.

16. Young, F. G.: The Anterior Pituitary Gland and Diabetes Mellitus, New England J. Med. **221**:635-646, 1939.

17. Allen, F. M.: Hyperinsulinism: Spontaneous and Artificial Hyperinsulinism, J. Clin. Endocrinol. **1**:595-603, 1941.

production of insulin is theoretically sound (see dextrose-insulin tolerance curve), but practice has been disappointing. Subtotal pancreatic resection in the absence of a demonstrable tumor has been singularly unsuccessful in the treatment of hyperinsulinism.

Operation should be done early in these cases, for obesity is a natural development of the eating habits of these patients, and the technical difficulties of operation on obese patients are obvious. Long-standing hyperinsulinism can produce permanent damage to the central nervous system,[18] and for this reason operation should not be too long delayed.

18. (*a*) Baker, A. B., and Lufkin, N. H.: Cerebral Lesions in Hypoglycemia, Arch. Path. **23**:190-201 (Feb.) 1937. (*b*) Baker, A. B.: Cerebral Lesions in Hypoglycemia: II. Some Possibilities of Irrevocable Damage from Insulin Shock, ibid. **26**:765-776 (Oct.) 1938. (*c*) Klein, F., and Ligterink, J. A.: Insulin and Cerebral Damage, Arch. Int. Med. **65**:1085-1096 (June) 1940. (*d*) Kerwin.[121]

CONCLUSION

With the report of 2 of our own cases and 10 from the literature we have raised the number of benign adenomas of the islets of Langerhans which have been successfuly removed at operation with recovery of the patients to 56.

A brief discussion of hyperinsulinism in its relationship to the endocrine system has been presented and the therapeutic implications stated. We believe that the study of this condition will be furthered if more attention is paid to the alterations produced in the other endocrine glands.

Surgical removal of these tumors is indicated as the most effective therapy, and this treatment is imperative in order to prevent damage to the central nervous system as a result of long-standing hypoglycemia.

The question of the cause of any new growth is challenging, but it seems doubly so in the case of a new growth which functions in the body's economy.

Medical College of Virginia, Hospital Division.

LESIONS OF MUSCLE IN SPIROCHETAL JAUNDICE (WEIL'S DISEASE; SPIROCHETOSIS ICTEROHEMORRHAGICA)

WALTER H. SHELDON, M.D.
ATLANTA, GA.

Few laboratories are equipped to perform the various procedures which may be needed for the diagnosis of spirochetal jaundice (Weil's disease; spirochetosis icterohemorrhagica). Larson,[1] in making a survey of leptospirosis among wild rats, concluded that multiple diagnostic methods should be employed since no single test always gave positive results in a sizable proportion of cases. Rather characteristic lesions in striated muscle in some cases of Weil's disease have been mentioned by Pick[2] and Jeghers, Houghton and Foley.[3] This report deals with lesions encountered in 16 biopsy specimens from muscles of the calf of 7 patients with Weil's disease seen recently at Grady Hospital.

REPORT OF CASES

One patient (case 7) was a white man, while the others were Negroes. All had a history of exposure to rats. Two patients (cases 1 and 5) worked as poultry dressers. One patient (case 2) was a fish cutter, 1 (case 4) had been digging ditches just before his present illness while 1 (case 6) had cleaned out a fish pond. One patient (case 3) was a housewife, who stated that her home was infested with rats. One patient (case 7) worked at a dairy where rats were numerous. The age and the sex distribution are shown in table 1.

Varying degrees of jaundice as well as enlargement of the liver were observed in every instance. The spleen was never enlarged. Muscular pains, particularly in the calves, were a constant feature in cases 1 through 6. This sign, however, was absent in case 7.

TABLE 1.—*Summary of Data on Seven Cases of Weil's Disease*

Case	Age	Sex	Highest polymorphonuclear Cells	Highest Nonprotein Nitrogen, Mg. per 100 Cc.	Highest Icteric Index	Agglutination L. icterohaemorrhagiae	Day of Disease
1	38	M	23,000	61	92	1:10	10th
						1:1,000	12th
						1:100	33d
2	35	M	36,850	150	84	1:40	7th
						1:2,650	17th
						1:1,000	25th
3	46	F	38,500	35.4	141	1:3,000	13th*
4	40	M	21,600	57.2	105	Negative	12th†
						Negative	14th†
						1:10,000	21st‡
5	37	M	19,300	41	55	1:10,000	8th‡
						1:100,000	15th‡
6	55	M	43,400	133	28.5	Negative	9th†
7	29	M	16,450	41	27	Negative	8th
						1:1,000	12th
						1:1,000	18th

* Leptospiras were demonstrated by dark field examination from the liver of a guinea pig inoculated with the patient's blood.
† Done with commercial antigen only.
‡ Done by the National Institute of Health; negative results were obtained with commercial antigen.

The principal laboratory data are shown in table 1.

The clinical course was mild in cases 3, 4 and 5. In cases 1, 2 and 7 the patients were more seriously ill. Relapses, which are common with this disorder, were noted clinically in cases 1, 2, 4 and 7. One patient (case 6) died on the third day in the hospital.

The pertinent changes noted at autopsy in case 6 consisted of hepatitis, tubular nephritis, icterus, fibrinous pericarditis and petechial hemorrhages in the pleura, the gastric, intestinal and bronchial mucosa and the renal pelves, consistent with Weil's disease. Attempts to demonstrate leptospiras by Levaditi's method were made on blocks from liver and kidney. Several suggestive structures were seen in the kidney, but it was felt that these were not unequivocal.

These 7 cases presented the clinical signs and symptoms of Weil's disease as discussed by Ashe, Pratt-

From the Departments of Pathology of Grady Hospital and Emory University School of Medicine.

Read at the Second Annual Meeting of the American Federation for Clinical Research, held at Chicago on June 12, 1944.

1. Larson, C. L.: Leptospirosis in Rats (R. Norvegicus) in and about Washington, D. C., Pub. Health Rep. **58**:944-955, 1943.

2. Pick, L.: Zur pathologischen Anatomie des infektiösen Icterus, Berl. klin. Wchnschr. **54**:451 and 481, 1917.

3. Jeghers, H. J.; Houghton, J. D., and Foley, J. A.: Weil's Disease: Report of a Case with Postmortem Observations and Review of Recent Literature, Arch. Path. **20**:447-476 (Sept.) 1935.

Thomas and Kumpe.[4] Agglutination tests gave positive results in all instances but case 6. It is of interest that agglutination tests gave negative results in cases 4 and 5 when done with commercial antigen (from Lederle Laboratories, Inc.) but that the same specimens gave a strongly positive result when examined by the National Institute of Health, where live organisms are used.

The agglutination test which gave a negative result in case 6 was done only with commercial antigen and on the ninth day of the disease. This test generally gives positive results only after the ninth or tenth day of the disease. The observations at autopsy, both gross and histologic, were consistent with Weil's disease. At present, however, no single morphologic feature or combination of features can be regarded as absolutely diagnostic. Only the demonstration of the organism in section is definite morphologic proof.

Dark field examination of blood and of urine gave negative results in all 7 cases. Guinea pig inoculation was done in cases 2, 3, 4 and 6. Leptospiras were demonstrated only in case 3, by dark field examination of the liver of 1 animal.

Material.—Sixteen biopsy specimens were obtained in 7 cases. In all instances a small fragment of the gastrocnemius muscle, approximately 1 cm. across, was removed under local anesthesia. Care was taken to infiltrate the tissues in such a fashion as to produce anesthesia in a fairly wide zone around the point from which the biopsy specimen was to be taken but to avoid infiltration of the tissue which was to be removed. In all instances the tissue was fixed within less than five minutes after removal. The tissue was fixed in both Zenker's fluid and solution of formaldehyde (10 per cent of the U. S. P. concentration), with the exception of 2 specimens, of which 1 was fixed only in Zenker's fluid and the other only in solution of formaldehyde. All Zenker-fixed material was stained with phloxine

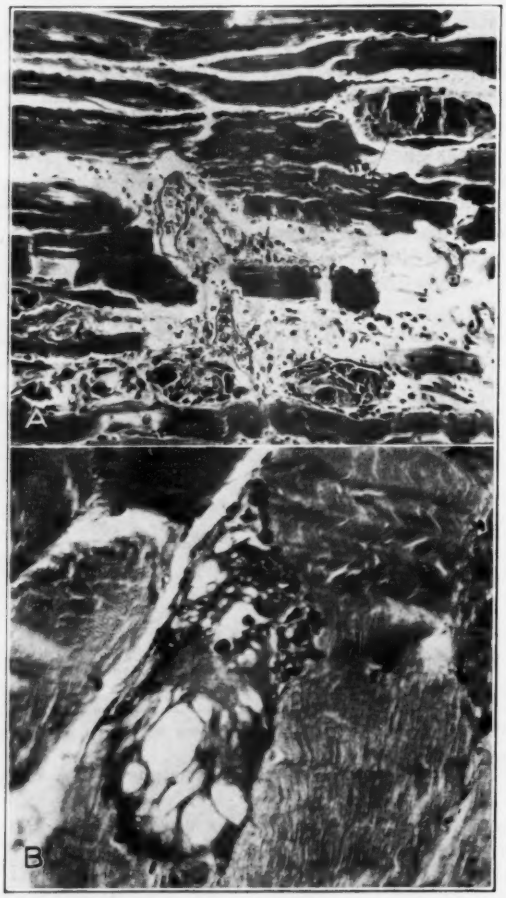

Fig. 1.—*A*, multiple focal areas of necrosis in striated muscle fibers. Most of the cells seen in the areas of necrosis are sarcoblasts, although the inflammatory cell infiltration in this case was unusually pronounced. Phloxine-methylene blue; × 120. *B*, cytoplasmic vacuoles in a portion of one muscle fiber, with proliferation of sarcoblasts at both ends of the lesion. Outside the lesion the cross striations of the involved muscle fiber are preserved. Phloxine-methylene blue; × 290.

4. Ashe, W. F.; Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's Disease: A Complete Review of American Literature and an Abstract of the World Literature; Seven Case Reports, Medicine **20**:145-210, 1941.

and methylthionine chloride (methylene blue), Mallory's phosphotungstic acid hematoxylin and Mallory's aniline blue. Turnbull's blue method for hemosiderin was used in some instances. Levaditi's method for the staining of spirochetes was employed on all material fixed with formaldehyde. Hematoxylin and eosin were used in the single case in which no Zenker-fixed tissue was available.

The lesions were shown clearly with routine fixatives and stains. Reasonable care should be taken not to traumatize the tissue during removal. It is advisable particularly in cases in which the condition is mild, to cut six or eight sections. This will minimize the chance of missing the lesions if they are sparse.

No grossly visible changes were noted in any of the specimens.

Histologic Changes.—The 16 biopsy specimens were arranged in chronologic order, according to the day of the disease on which they were taken. The day of the disease was counted from the first appearance of symptoms noted by the patient. When arranged in this fashion the specimens ranged from the tenth to the sixty-sixth day of the disease (table 2).

Table 2 also shows the number of biopsy specimens taken from each patient.

When the specimens were studied in this order, the life history of the lesions could be followed readily. There were, of course, certain variations, according to the severity of the disease, in the individual cases. These variations, however, were quantitative rather than qualitative.

The lesions varied in number and extent. With mild forms of the disease, such as were found in cases 3, 4 and 5, relatively few small lesions were seen, while with more severe forms, as in cases 1, 2, 6 and 7, the lesions were numerous and larger. They always involved only a part of one muscle fiber. Sometimes

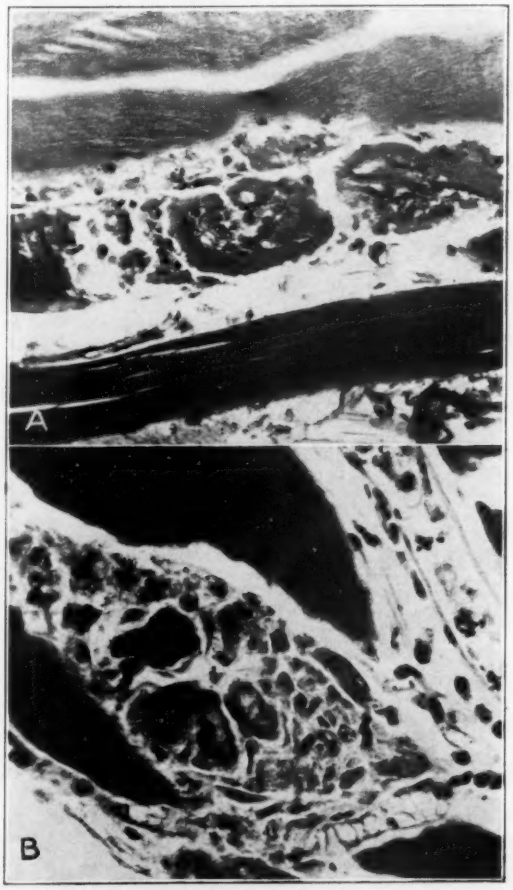

Fig. 2.—*A*, early necrosis in the cytoplasm of one muscle fiber. The transition between vacuolation and necrosis is visible. There is no significant inflammatory cell response. Phloxine–methylene blue; × 280. *B*, sarcoblasts surrounding fragments of necrotic muscle. Inflammatory cells are few. Phloxine-methylene blue; × 460.

TABLE 2.—*Day of Disease When Biopsy Specimen Was Taken*

Case	Day
1	10, 17, 24, 31
2	17, 24, 35, 66
3	13, 36
4	13, 25
5	8*
6	13
7	11, 29

* The appearance of the lesion suggests that the disease may have been of longer standing than indicated by the history. The high agglutination titer (1:10,000) supports this impression.

two or even three adjoining fibers showed focal involvement. Rarely several independent foci were found in one single fiber. These sometimes became confluent, simulating a single large focus which involved a considerable portion of a muscle fiber (fig. 1 *A*).

The earliest visible change consisted in the appearance of small and medium-sized vacuoles within a portion of the cytoplasm of the striated muscle fiber. These vacuoles tended to become confluent (fig. 1 *B*). This stage is well illustrated by Jeghers and coworkers[3] in figure 1 of their report. Simultaneously, the cytoplasm of the muscle fiber in the involved area lost its cellular detail. The longitudinal fibrils and the cross striations disappeared, and only fragmented masses of homogeneous or irregularly granular acidophilic material remained. The margins of the lesion were frayed and irregular but distinct (fig. 2 *A*). The myofibrils and the sarcoplasm of the adjoining portions of the muscle fiber did not show any demonstrable changes. At this stage, no significant cellular reaction demarcated the lesion from the uninvolved portion of the fiber and generally no changes were noted in the interstitial connective tissue or in the adjoining capillaries, which, however, were congested. Only in 2 instances a tiny recent hemorrhage into a muscle fiber was seen (fig. 4). The first sign of cellular reaction consisted in the appearance of nuclei within the uninvolved portion of the fiber at both ends of the lesion. These nuclei were situated immediately beneath the sarcolemma sheath. They were rather large, oval and vesicular and had a prominent nucleolus (fig. 1 *B*). Their number increased rapidly. Mitosis was seen often, but there were also indications of amitotic division. These elements extended along the sarcolemma sheath at the lateral margins of the lesion. Here they sometimes tended to assume a pearl-string-like or multinucleated syncytial arrangement. This was essentially the picture as seen on the tenth to the thirteenth day of the disease.

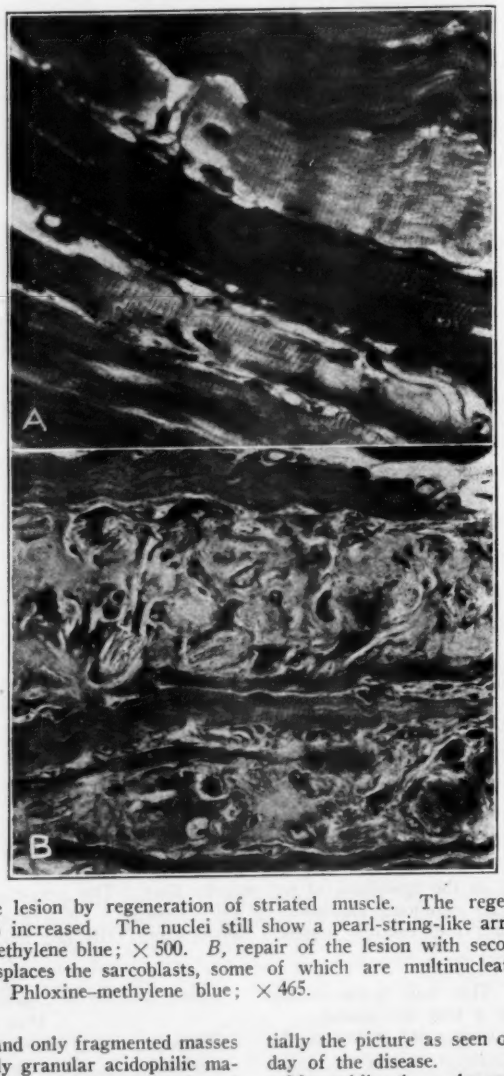

Fig. 3.—*A*, repair of the lesion by regeneration of striated muscle. The regenerated fiber stains darker, and the number of nuclei is increased. The nuclei still show a pearl-string-like arrangement. Note the absence of any fibrosis. Phloxine–methylene blue; × 500. *B*, repair of the lesion with secondary fibrosis. The lighter-staining connective tissue displaces the sarcoblasts, some of which are multinucleated while others show segmented longitudinal fibrils. Phloxine–methylene blue; × 465.

Meanwhile, these elements had become separate cells displaying the characteristics of sarcoblasts. They showed varying amounts of basophilic cytoplasm. Their shape ranged from round to elongated fusiform or often stellate with two or three processes. Coming from both ends, as well as from the margins of the lesion, they had invaded the area of necrotic muscle, which by now consisted of hyaline fragments. Some of the sarcoblasts had begun to encircle the individual

fragments of necrotic material, and in this process some large multinucleated cells had formed. Occasionally, some sarcoblasts appeared to have formed small niches at the margin of the fragment of necrotic muscle (fig. 2 *B*). This appearance suggested a digestion of the necrotic tissue. Polymorphonuclear leukocytes were seen infiltrating the necrotic area, but on the whole the inflammatory cell infiltration was not striking. No significant changes were noted in the adjoining interstitial connective tissue and capillaries. This was essentially the picture seen in the tissue removed on the seventeenth day of the disease.

At this stage, only slight new formation of myofibrils could be discerned. This consisted in the appearance of granules within the cytoplasm of the proliferating sarcoblasts, as seen with the phosphotungstic acid hematoxylin stain. These granules were arranged in a definite pattern longitudinal to the long axis of the cells. Longitudinal fibrils segmented at regular intervals by dark granules appeared, and cross striations became visible in the manner described by Wolbach.[5]

cells appeared in the interstitial connective tissue adjacent to the involved muscle. This was associated with some proliferation of fibroblasts, which grew into the area of necrosis and participated in the repair of the lesion. On the whole, however, the degree of inflammatory cell infiltration was slight and never formed a prominent feature of the lesion. The capillaries adjoining the lesion, as well as the larger vessels elsewhere throughout the section, did not display any demonstrable changes. This was the appearance of the lesion on the twenty-fourth day of the disease.

The latter stages of the process, as seen in the biopsy specimens obtained on the thirty-fifth and sixty-sixth day of the disease, showed the progress of repair by fibrosis. The fibroblasts had become more prominent and had begun to deposit collagen. The latter increased and appeared to encroach on the sarcoblasts, which showed signs of atrophy (fig. 3 *B*). In addition, but apparently not related to the scarring, small amounts of light brown refractile pigment deposited in granules had become visible in some of the sarcoblasts encircling the remaining fragments of necrotic muscle. This pigment stained blue with Turnbull's blue method for hemosiderin.

Fig. 4.—Early lesion with hemorrhage into one muscle fiber (left lower corner) and vacuoles in another (right upper corner). Other muscle fibers (lower center and right upper corner) show advanced repair. The recent lesions coincided with a clinical relapse lasting from the twenty-fourth to the twenty-ninth day of the disease in case 2. Phloxine-methylene blue; × 275.

This repair became rapidly more active. In the cases in which the foci of necrosis had been few and small and the clinical course had been rather mild, the repair had been almost completed in a period ranging from the twenty-fifth to the thirty-sixth day of the disease. A few muscle fibers were seen which often appeared thinner than normal. Their cytoplasm stained rather dark basophilic. The nuclei beneath the sarcolemma sheath were more numerous than in normal muscle fibers and displayed some persistence of the pearl-string-like arrangement (fig. 3 *A*). No changes were noted in the adjacent interstitial connective tissue and capillaries.

Thus the lesion had been repaired by regeneration of the striated muscle without significant participation of the adjacent interstitial connective tissue. Therefore, no appreciable fibrosis and scarring had occurred.

When, however, the disorder was clinically more severe and complicated by one or several relapses, an inflammatory cell infiltration of lymphocytes and plasma

Thus in the more severe lesions repair was accomplished by fibrosis.

In every case a large number of sections stained with Levaditi's method for spirochetes was searched for the organism. In only 2 instances structures suggestive of leptospiras were seen. It was felt, however, that these were not unequivocal.

COMMENT

The morphologic features of the lesions in the muscle correlated well with the clinical course. Early but definite lesions were present on the tenth day of the disease in case 1. Clinical relapses, which are common with this disorder, were marked by the appearance of new lesions besides the already existing older ones (fig. 4). These new lesions followed the same sequence of events as described. This is well shown in case 1, in which the patient had a relapse with a rise

5. Wolbach, S. B.: Centrioles and the Histogenesis of the Myofibrils in Tumors of Striated Muscle Origin, Anat. Rec. **37**:255-262, 1928.

of temperature to 102 F. on the twenty-third and twenty-fourth day of the disease. The biopsy specimen taken on the twenty-fourth day of the disease showed early lesions of the type seen on the thirteenth day of disease in the other patients besides the older lesions which already displayed advanced repair. The taking of a biopsy specimen on the twenty-fourth day in case 2 coincided with a rise in temperature to 104 F. from the twenty-fourth to the twenty-ninth day. This specimen showed a few recent lesions of the earliest type besides older ones. A similar picture was seen in a specimen taken in case 4 on the twenty-fifth day, when the patient's temperature rose from normal to 100 F.

Morphologically the lesion in the muscle appeared to be rather typical. The small focal distribution of the lesion and the absence of significant hemorrhage differentiated it from Zenker's degeneration. This had already been pointed out by Jeghers and his co-workers,[5] who stressed the characteristic appearance of this lesion as compared with other lesions of muscle. The absence of vascular changes distinguished this lesion from those found in the muscles in cases of rickettsial infections. Control sections of gastrocnemius muscle were taken at autopsy in 2 cases of subacute yellow atrophy of the liver after arsphenamine treatment, in 1 case of nonobstructive biliary cirrhosis of the liver, in 2 cases of pneumococcic pneumonia with septicemia, in 1 case of staphylococcic septicemia and in 1 case of subacute bacterial endocarditis of the mitral and aortic valves. No lesions resembling those of Weil's disease were observed.

It is an acknowledged fact that Weil's disease can be diagnosed only by laboratory tests. These consist of dark field examination of the blood, urine or duodenal washings for demonstration of the organism, agglutination reaction, animal inoculation or culture. The findings in these 7 cases and those described in the literature suggest that the lesions in the muscles of the calf might be a constant and reliable feature of this disease. Since a biopsy specimen of the muscles of the calf can be taken without undue difficulty, this procedure is suggested as a possible aid in the diagnosis of Weil's disease.[6]

SUMMARY AND CONCLUSIONS

Lesions in the muscles of the calf were encountered in 16 biopsy specimens in 7 cases of spirochetal jaundice (Weil's disease; spirochetosis icterohemorrhagica).

The morphologic characteristics of these lesions are considered rather typical of this disease. The observations reported suggest that these lesions may be a constant feature of this disorder.

Biopsy of the muscles of the calf is suggested as a useful measure in the diagnosis of Weil's disease.

---

6. After this report was submitted for publication biopsy specimens of muscles were obtained from 12 other patients with suspected Weil's disease.

In 5 cases lesions of Weil's disease were found, but in only 1 did the patient show a positive reaction to an agglutination test. In another the reaction to an agglutination test was negative with commercial antigen, while the single blood sample examined by the National Institute of Health showed a positive reaction for L. icterohaemorrhagiae with a titer of only 1:100. The agglutination test in the other 3 cases always gave negative results.

In 1 of the remaining 7 cases Weil's disease was proved by an agglutination test. A single biopsy specimen of muscle was reported as showing nothing significant, but the tissue was too severely traumatized during its removal to permit adequate histologic study. A biopsy specimen from a patient with proved typhus was first considered indicative of Weil's disease, but further sections clearly revealed the typical vascular lesions of rickettsial infection.

Infectious hepatitis (3 cases), reaction to arsphenamine therapy (1 case) and atypical pneumonia (1 case) were found in the remaining 5 cases in which biopsy specimens gave negative results.

Progress in Internal Medicine

VASCULAR DISEASES

TENTH ANNUAL REVIEW

THEODORE R. VAN DELLEN, M.D.; GEORGE W. SCUPHAM, M.D.;
GEZA DE TAKATS, M.D., AND EDSON FAIRBROTHER FOWLER, M.D.
CHICAGO

REVIEW OF SOME OF THE RECENT LITERATURE

BY DR. VAN DELLEN AND DR. SCUPHAM

During the past year there has been a definite decline in the number of publications on peripheral vascular disease. Many noted and consistent workers in this field are obviously devoting their time and talent to the war effort. Some of these men have already collected and published valuable data obtainable only under wartime conditions. Publications associated with the physiology of vascular disease are not as numerous as in previous years, and statistical data on large series of cases are conspicuously absent. Attention should be called to the anticoagulants, to fluorescein and to recent observations on periarteritis nodosa. Therapy has been totally neglected. As in the past, this review should not be considered complete, since many deserving articles have possibly been missed.

PHYSIOLOGY

Diagnostic Tests.—Naide [1] recently reported a test for estimating vascular tone. This was determined by measuring the rate of fall in temperature of the extremities during a cold period and the rate of rise during a period of application of moderate heat to the trunk. Studies were performed in a constant temperature room at 20 C. Surface temperatures of the fingers and toes were recorded. The importance of readings of finger temperature lies in the fact that normally there is less tone in the vessels of the fingers than in those of the toes, and by observing the response to cold and to heat at these sites a gradient of vascular tone or ratio of vascular response in the feet to that in the hands can be determined. Moderate heat was used to prevent most normal persons from having vasodilatation, thereby distinguishing those who were slightly vasospastic. Information of this nature was obtained for 53 normal persons, and a simple table was arranged in which these subjects were classified on the basis of vascular tone. Seven groups were obtained, ranging from persons with low to persons with high vascular tone. Patients with vascular disease were found to fall in the groups with vascular tone approaching high values. Sixteen of 17 patients with thrombophlebitis were also in the vasospastic groups. Nine of 32 patients with thromboangiitis obliterans were in the group with low vascular tone. Various other studies were done in association with this test. The author was able to distinguish whether vasodilatation or vasoconstriction in different persons was located in large or small arteries by comparing the oscillometric index with the surface temperature. This test opened up a new approach to vascular study and was worthy of consideration for all interested in this problem.

Rinzler, Travell and Civin [2] correlated Atlas' oscillometric index with other objective evidences of vascular disease, namely, surface temperature and changes shown by roentgen examination of the vessels of the lower extremity. This index was described in a previous review. Studies were performed on 84 ambulatory patients. A correlation of the data obtained by these three laboratory aids (oscillometry, determination of surface temperature and roentgenography) showed that as the oscillometric index decreases, the incidence and extent of calcification of the lower extremity and the incidence of abnormal cutaneous temperatures increase. In contrast to the work of Atlas, these authors concluded that the index can be lowered from 1.0 to 0.75, as in their studies readings above the latter figure always indicated adequate arterial function in the lower extremity. An index below 0.75 in their opinion is pathologic and compatible with sclerotic changes, and a value below 0.3 indicates extensive calcification and probable ad-

From the Department of Medicine, Northwestern University Medical School; the Department of Surgery, the University of Illinois College of Medicine, and the Circulatory Group, St. Luke's Hospital.

1. Naide, M.: A Test for Vascular Tone in Humans and Its Application to the Study of Vascular Diseases with Special Reference to the Etiology and Prevention of Thrombophlebitis, Am. J. M. Sc. **207**:606 (May) 1944.

2. Rinzler, S. H.; Travell, J., and Civin, H.: The Oscillometric Index: An Aid in Evaluating the Arterial Status of the Lower Extremities, Arch. Int. Med. **73**: 241 (March) 1944.

vanced occlusive arterial disease. The authors discussed oscillometric readings in general and concluded that a reading of more than 4 at the ankle or more than 2 at the foot nearly always indicates normal arterial flow. A reading of less than 1 at the ankle or 0 at the foot is in their opinion indicative of occlusive arterial disease.

Foregger [3] studied the effect of the commoner anesthetic agents on the surface temperature of normal persons. A maximum increase with full vasodilatation of the peripheral vessels was produced by inhalation of nitrous oxide, ethylene, cyclopropane, ether and chloroform. This phenomenon occurred in the first phase of anesthesia if maintained for several minutes. As a rule there was no fall in arterial pressure. Maximum dilatation also followed spinal or local block anesthesia. Lumbar sympathetic block was not found to be entirely satisfactory, as it was painful and uncertain. Intravenous injection of pentothal sodium produced a good response, and only a light plane of anesthesia was required. The author presented excellent charts, which can be considered as records of normal responses to the drugs administered.

Two preparations have recently been introduced for visualizing the arterial tree in postmortem specimens. These are of value not only because they are radiopaque but because they facilitate dissection. Tobin [4] used a pigmented liquid latex solution combined with a mixture of ethyl esters of iodophenylundecylic acid (pantopaque). Epstein [5] employed a mixture of lead tetroxide (red lead) and glue. He found this most useful in studying the blood supply to lymph glands and nerve tissue.

Circulation Time.—The intravenous administration of fluorescein for measuring the circulation time was reported in last year's review. Additional articles have been noted which elaborated on its usefulness or described improvement in technic. Lange and Boyd [6] measured the arm to face circulation time in 212 normal adults. The time ranged between fifteen and twenty seconds, the majority of values being between fifteen and seventeen and five-tenths seconds. The appearance of fluorescein in the lip under a special source of long wave ultraviolet radiation was used as the end result. These readings are in keeping with those obtained by most methods but slower than those obtained by others. The observations are consistent with results of previous investigations of the circulation times in the aged, during fever or work, and in the presence of failure of the right side of the heart, asthma, hyperthyroidism, hypothyroidism and anemia. They also demonstrated that fluorescein can be used to determine the velocity of the flow of blood to different parts of the body. The average time of circulation to the conjunctiva, lips, rectum and foot was ten, fifteen, eighteen and twenty-three seconds, respectively. The time to the conjunctiva was the shortest, but for obvious reasons this area was not recommended. The authors also compared their results with those obtained with acetylene inhalations, using the latter to measure the time which elapsed until all blood in rapid circulation had passed the lungs at least once. This was labeled as the "slowest circulation time."

Sicher [7] reported on his experience with fluorescein. Since his light was small, only a part of the body was illuminated at one time. Readings were routinely taken from the lips, fingers, base of the toes and other structures, depending on the pathologic condition being studied. The circulation time was prolonged in cases of peripheral vascular disease, and in certain cases fluorescein was not detected in an ischemic toe after ten minutes' observation. The author stressed the fact that fluorescence does not occur until blood bearing the dye has made its way well up into the arterioles and capillaries of the skin. It is essentially a surface phenomenon and directly influenced by possible variations in arteriolar and capillary tonicity, in dilatation or constriction. The observations indicate that the results of the test coincide well with the physical findings of peripheral arterial obstruction. The article is followed by a few statements concerning the physical and biophysical nature of the phenomenon of fluorescence.

In a more recent article, Lange and Krewer [8] described an instrument for the objective measurement of the fluorescence of the skin and organs and the determination of circulation time and capillary permeability. This instrument is

3. Foregger, R.: Surface Temperatures During Anesthesia, Anesthesiology **4**:392 (July) 1943.

4. Tobin, C. E.: A Radiopaque Liquid Latex Injection Medium for Blood Vessels, Am. J. Roentgenol. **51**:386 (March) 1944.

5. Epstein, J.: A Method for Visualizing the Blood Vessels of Nerves and Other Tissues, Anat. Rec. **89**: 65 (May) 1944.

6. Lange, K., and Boyd, L. J.: Objective Methods to Determine the Speed of Blood Flow and Their Results (Fluorescein and Acetylene), Am. J. M. Sc. **206**:438 (Oct.) 1943.

7. Sicher, W. D.: Circulation Time of the Extremities Using Intravenous Administration of Fluorescein, Proc. Staff Meet., Mayo Clin. **18**:515 (Dec. 29) 1943.

8. Lange, K., and Krewer, S. E.: Dermofluorometer: Instrument for Objective Measurement of Fluorescence of Skin and Organs and Objective Determination of Circulation Time and Capillary Permeability, J. Lab. & Clin. Med. **28**:1746 (Nov.) 1943.

called the dermofluorometer. It consists of two parts. The first is a small light emittting blue rays which are directed toward the skin at an angle. The reflection of this light is registered on the second part, which contains a phototube. This reflected light is yellow-green, depending on the fluorescence of the blood stream. Filters allow only the proper light to come into contact with the phototube. This instrument deflects light in direct proportion to the concentration of fluorescein present. Objective measurements are thus possible for determining both circulation time and capillary permeability.

Effect of Drugs.—Stead and Warren [9] injected histamine into the brachial artery in human beings and noted that it increased the permeability of capillaries supplied by this artery. A rapid loss of protein from the plasma was detected by comparing the blood draining from the part before and after the injection. The hematocrit reading and the hemoglobin concentration increased greatly, while the protein concentration rose only slightly. The authors failed to notice a similar action in uninjured tissue in the usual types of shock.

The variations in blood flow to the fingers following the intramuscular injection of nicotinic acid, priscol (2-benzyliminazoline), eupaverine (methylenedioxybenzylmethylmethylenedioxyquinoline) and prostigmine methylsulfate were discussed by Introzzi and his colleagues.[10] Studies were performed on 17 normal persons and 4 patients with Raynaud's syndrome. The blood flow was measured with the plethysmograph. The results were inconstant, especially for normal subjects. The temperature of the skin rose considerably with eupaverine and priscol, and the central temperature generally decreased with nicotinic acid. For 2 of the patients with Raynaud's syndrome prostigmine was found effective, but the authors considered the series too small to be of significance.

Redisch and Pelzer [11] studied the peripheral capillaries of patients with migraine before and after the intravenous administration of 0.25 to 0.5 mg. of ergotamine tartrate. Studies were made with the capillary microscope. Impaired visibility of the surface outlines of the capillaries was observed during 142 attacks of migraine in 118 patients. After the administration of ergotamine tartrate to 23 of these patients changes were noted in 20. This led the authors to believe that a disturbance in water balance might exist during the attack of migraine, and experiments were performed after the administration of 1,500 cc. of water. Fourteen of the 15 patients thus studied were found to have an abnormal "excess secretion" of urine. As this excess secretion subsided, a migraine headache developed in 21 of the 29 experiments. Headaches did not develop in 4 of the patients who had a normal response to the ingestion of water. When ergotamine tartrate was injected during the height of the water-induced headaches, relief was obtained, but usually associated with diuresis and profuse perspiration. These results are difficult to explain, but the authors believe that a relationship exists between fluid balance, the state of the peripheral capillaries and migraine attacks.

Levinson and Essex [12] made direct observations on the reaction of the small blood vessels in the rabbit's ear to epinephrine, ephedrine, ergotoxin and pitressin before and after denervation. Studies were made after stimulation of the auricular nerves and cervical sympathetic chain. An attempt was also made to correlate the reactions of the blood vessels with necropsy evidence of regeneration, in an effort to determine the function of the nerves innervating these vessels. The vessels were observed through a Clark transparent chamber, which has proved suitable for this type of study. Epinephrine caused a constriction of the arterioles accompanied by a slight narrowing of the venules. Ephedrine produced a similar response, but there was evidence of a refractoriness to repeated doses. Pitressin in the dosage used (0.1 pressor unit per kilogram of body weight) resulted in the most pronounced vasoconstriction, but refractoriness to repeated injections was also noted. Ergotoxin blocked the vasoconstrictor action of epinephrine. Stimulation of the cervical sympathetic chain produced a constriction of the arterioles in the window more consistently than did stimulation of the dorsal or great auricular nerves. The denervated vessels became hypersensitive to epinephrine and seemed to regain their tone after this procedure. The blocking action of ergotoxin was also altered by denervation.

Tobacco.—There is sufficient evidence to date to substantiate the fact that smoking will de-

9. Stead, E. A., Jr., and Warren, J. V.: The Effect of the Injection of Histamine into the Brachial Artery on the Permeability of the Capillaries of the Forearm and Hand, J. Clin. Investigation **23**:279 (March) 1944.

10. Introzzi, A. S.; Cabanne, E. A., and de Soldati, L.: Plethysmographic Studies on the Action of Various Drugs on Caudal Flow of Blood, Rev. argent. de cardiol. **9**:230 (Sept.-Oct.) 1942.

11. Redisch, W., and Pelzer, R. H.: Capillary Studies in Migraine: Effect of Ergotamine Tartrate and Water Diuresis, Am. Heart J. **26**:598 (Nov.) 1943.

12. Levinson, J. P., and Essex, H. E.: Observations on the Effect of Certain Drugs on the Small Blood Vessels of the Rabbit Ear Before and After Denervation, Am. J. Physiol. **139**:423 (July) 1943.

crease the flow of blood to the extremities. The mechanism of action and the causative factors are still questioned, but the current opinion still favors nicotine and its effect on the sympathetic nervous system. Evans and Stewart [13] studied this problem and measured the peripheral blood flow by means of a modification of the method of Hardy and Soderstrom. Observations were made on normal persons not only after they had smoked the standard type of cigaret but also after their smoking denicotinized cigaret and cigarets made from cornsilk and after their smoking through a water pipe. A decrease in blood flow occurred in every instance, regardless of the type of cigaret smoked. After the cessation of smoking, the flow usually decreased and by the end of thirty minutes returned to normal. In addition, the blood pressure, pulse rate and rectal temperature increased regardless of the type of cigaret smoked, and the temperatures of the skin of the hands and feet usually decreased. The effects on the basal metabolic rate and on the electrocardiogram were either too slight or too variable to be of significance. Since these changes occurred after the smoking of the cigarets which did not contain nicotine as well as of those which did, it was natural for the authors to conclude that nicotine was not the contributing factor. They suggested that stimulation of the sympathetic nervous system brought about by the irritating effect of smoke on the respiratory tract might be responsible for the changes observed. From the results of this study it appeared that smoking of any type of cigaret, regardless of its nicotine content, should be avoided in the presence of peripheral vascular disease.

Blood Flow.—After a unilateral peripheral nerve block for the release of arterial tone, it is not an uncommon observation to note a concomitant vasoconstriction in the opposite extremity, providing adequate dilatation is produced on the paralyzed side. Neumann and his colleagues [14] reiterated this observation and offered a logical explanation. They compared the vascular changes in the small vessels of the toes with those in the fingers following spinal anesthesia. They also compared the changes in the fingers of the two hands following a local block of one stellate ganglion. The pulse wave in the digit devoid of its sympathetic supply increased and the alpha waves decreased, but in the control both waves decreased to one-half or one-quarter their former size. Measurements were made with the pneumoplethysmograph of Turner. There were no changes in the blood pressure or pulse rate during the period of spinal or regional anesthesia. These phenomena were not noted when occlusive vascular disease was present. The authors considered the mechanism to be one of adjustment, possibly of compensation, through efferent pathways of the sympathetic system. Paralysis of these nerves permitted maximal expansion of the small blood vessels and interrupted the pathways of stimuli necessary for the formation of prominent alpha waves. At the same time, increased sympathetic outflow to certain other vascular fields resulted in vasoconstriction of such intensity as to produce small pulse waves and to inhibit the relaxation apparently necessary for the development of alpha waves.

Stewart and Evans [15] studied the peripheral blood flow under basal conditions in 34 normal men in the third decade of life. Measurements of blood flow were made by a modification of the method of Hardy and Soderstrom. In using this method certain data were required, namely, cutaneous temperatures at 11 points on the anterior surface of the body, rectal temperature, oxygen consumption, height and body weight. The average peripheral blood flow was 52 cc. per square meter per minute at 27 C. The flow at room temperatures of 25 C. showed a range from 8 to 78 cc. per square meter per minute and at 27 from 34 to 127 cc. per square meter per minute. The flow usually varied in the same direction as the basal metabolic rate. The blood pressure and pulse rate were normal in each instance, and there were no differences in the averages for the subjects who were studied at 25 C. and those studied at 27 C.

The rate and control of blood flow through the skin of the upper extremities were recently computed by Goetz.[16] Studies were performed on 800 persons, and the determinations were made with the optical plethysmograph. This apparatus is similar to the finger plethysmograph described by Johnson. It is extremely sensitive and capable of registering not only the actual volume of the digits (skin) but the shape and height of the individual volume pulse. He found the pulse volume in the digits of normal warm-handed subjects to vary between 0.003 cc. during full constriction and 0.025 cc. at full dilatation. The height of the pulse volume was considered a more sensitive measure of vasomotor tone and of

13. Evans, W. F., and Stewart, H. J.: Effect of Smoking Cigarets on Peripheral Blood Flow, Am. Heart J. **26**:78 (July) 1943.

14. Neumann, C.; Sellers, E. A.; Rovenstine, E. A.; Cohn, A. E., and Rule, C.: Influence of Spinal and Regional Anesthesia upon Vasoconstriction and Vasodilatation of Small Peripheral Blood Vessels, Proc. Soc. Exper. Biol. & Med. **53**:159 (June) 1943.

15. Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow Under Basal Conditions in Normal Male Subjects in Third Decade, Am. Heart J. **26**:67 (July) 1943.

16. Goetz, R. H.: Rate and Control of Blood Flow Through Skin of Upper Extremities, South African J. M. Sc. **8**:65 (Feb.) 1943.

the potency of the arterial tree than most methods used for similar study. Comparing it with surface temperature, Goetz showed that when the latter reached the normal vasodilating level tracings of the pulse volume might demonstrate a decreased flow indicative of organic vascular disease. The rate of blood flow in the fingers of normal subjects was measured by means of the venous congestion test. This rate varied between 3 cc. per minute for 100 cc. of tissue during maximal constriction and 94 cc. during dilation. The rate of blood flow in the skin of the terminal phalanx was found to exceed that of the skin of the other phalanges.

Barcroft and Edholm [17] described the variations in blood flow of the forearm as a result of changes in temperature of the surrounding water in the plethysmograph. Studies of deep muscle temperature were also performed. Readings were obtained for a two hour period with water temperatures ranging from 13 to 45 C. The average values for blood flow in the forearm ranged from 0.5 cc. per hundred cubic centimeters of forearm per minute at 13 C. to 17.6 cc. at 45 C. The flow-time relations fell into three groups: 1. At 13.0 to 35.0 C. there was a slight decrease in flow during the two hour period, which was not conspicuous except in the first fifteen minutes. 2. At 37.0 to 45.0 C. the flow increased to a maximum in about one hour and then decreased steadily. 3. At 45 C. there was an increase to a maximum in thirty to forty-five minutes and the flow then remained constant. The authors also noted that spontaneous fluctuations in blood flow were more frequent at higher temperatures. The deep muscle temperature taken from the middle of the upper part of the forearm ranged from 18.0 C. after two hours' immersion at 13.0 C. to 39.0 C after thirty minutes' immersion at 42.5 to 45.0 C.

The blood flow patterns of various arteries were optically recorded by Shipley, Gregg and Schroeder [18] with an improved orifice type flow meter. These patterns were found to be characteristically distinctive of a given artery and its bed. For heteronymous arteries the pattern exhibited wide variations in magnitude, timing, direction and rate of flow but showed similarity of contour to the respective pressure pulses of the arteries. Back flow components existed in the femoral and axillary arterial flow and less frequently in the common carotid pattern, but the renal, hepatic and superior mesenteric arteries exhibited only a forward flow. This study lends itself to a qualitative evaluation of differences among the flow patterns of the same or of different arteries under various physiologic conditions.

The effect on the peripheral circulation of a period of relative anoxia was studied in a series of 25 normal subjects by Abramson and his associates,[19] using the venous occlusion plethysmograph. Anoxia was obtained by the inhalation of an oxygen-poor gas mixture (10 per cent oxygen and 90 per cent nitrogen) for periods of ten to twenty-seven minutes. During these periods they noted a small but definite increase in the rate at which blood flowed through the forearm and leg and generally a decrease in the circulation in the hand. In view of the fact that the vessels in the hand respond to all types of vasoconstricting stimuli, the results obtained during the period of anoxia were not considered greatly significant. Associated with the increase in the blood circulating through the forearm and leg were a significant augmentation in pulse rate, a slight elevation of systolic blood pressure and variable changes in the rate of respiration. The circulatory response to a period of exercise during the inhalation of the oxygen-poor gas was also compared with that obtained under normal circumstances. The results were interpreted to indicate that the compensatory adjustments to work in a state of relative anoxia were not as adequate as those elicited normally.

Himmelsbach [20] studied the blood flow in drug addicts. He used the venous occlusion plethysmographic method of Hewlett and Van Zwaluwenburg. The resting blood flow to the hands of morphine addicts and former addicts was found to be subnormal, whereas that of marihuana users was normal. Morphine was found to cause a significant increase in the rate of blood flow to the hands of addicts, of former addicts and of normal controls. The total increase to the hand in the first hour after the injection was greater with 10 and 20 mg. than with 40 and 60 mg. Demerol hydrochloride (the hydrochloride of the ethyl ester of 1-methyl-4-phenylpiperidine-4-carbonic acid) also increased the blood flow to the hand. These results are of interest from the vascular standpoint, but the author implied, so far as the addiction problem was concerned, that the former addict was tense and morphine relieved this state through a depression of the sympathetic division of the ner-

17. Barcroft, H., and Edholm, O. G.: The Effect of Temperature on Blood Flow and Deep Temperature in the Human Forearm, J. Physiol. **102**:5 (June 30) 1943.

18. Shipley, R. E.; Gregg, D. E., and Schroeder, E. F.: An Experimental Study of Flow Patterns in Various Peripheral Arteries, Am. J. Physiol. **138**:718 (April) 1943.

19. Abramson, D. I.; Landt, H., and Benjamin, J. E.: Peripheral Vascular Response to Acute Anoxia, Arch. Int. Med. **71**:583 (May) 1943.

20. Himmelsbach, C. K.: Studies on the Relation of Drug Addiction to the Autonomic Nervous System: Results of Tests of Peripheral Blood Flow, J. Pharmacol. & Exper. Therap. **80**:343 (April) 1944.

vous system. Larger doses tended to evoke counter action.

Studies on the surface temperatures of persons with induced vitamin B deficiencies were recently reported by Roth and her colleagues.[21] These were performed on 8 subjects under controlled environmental, postural and metabolic conditions. In no case did deficiencies in thiamine, riboflavin and other components of the vitamin B complex show any degree of vasomotor disturbances as evidenced by measurements of cutaneous temperature and determinations of rates of cooling and warming of body tissue.

Denervation.—Observations were made by Essex and associates[22] on the blood flow in the femoral arteries of a dog at intervals over a period of ten years and two months. Blood flow was measured in both femoral arteries simultaneously with the area under infiltration anesthesia before and after sympathetic ganglionectomy and at various times up to ten years and two months thereafter. Whereas the flow was twice as great in the left or sympathectomized limb as it was in the right, or control, limb fifteen days and also ten months and twenty-five days after the sympathectomy, the flow was almost the same in the two limbs nine and also ten years after the operation. The vessels of the sympathectomized leg were found to be hypersensitive to epinephrine more than nine and ten years following sympathectomy. This was demonstrated by injectiong a small amount of epinephrine hydrochloride, which caused so much constriction of the vessels of the sympathectomized side that the flow was nil for at least two minutes. The flow on the control side determined at the same time was only slightly altered. Simultaneous plethysmographic records of the two hindfeet further confirmed the observations on blood flow, since there was a transient decrease of the volume of the innervated foot but a prolonged decrease of that of the denervated foot in response to small doses of epinephrine. Histologic examination of a toe from each hindfoot showed that the arterioles of the left, or sympathectomized, foot had undergone hypertrophy. This was confined to the muscularis coat of the vessels. The vessels of the control side did not show this change.

Richards[23] reported at length his observations of the vasomotor disturbances in the hand following a division of a peripheral nerve. He used the surface temperature as an index of vasomotor response. The results were divided into two phases: an initial phase of vasodilatation, due to the interruption of the sympathetic vasoconstrictor fibers, and a second, but permanent, phase, in which the temperature of the area approximated that of its environment. There was no clearcut distinction in time between these two phases. Although Richards was unable to understand the factors responsible for the change to the cold phase, he believed that such conditions as lowering of local metabolism, sensitization of denervated blood vessels to circulating epinephrine and loss of afferent nerve fibers responsible for the "axon reflex" probably played a significant role.

Richards also noted that a digit which was incompletely denervated might show an almost normal reflex vasomotor activity, whereas a completely denervated digit does not respond reflexly to changes in body temperature but responds to the local metabolic needs of the tissues. Studies on denervated limbs have been done before, and in general their findings have been in agreement with those of Richards. The exact role played by various nerve structures is not entirely settled. Doupe[24] has recently published a series of articles on his observations on subjects with preganglionic and ganglionic sympathectomies and patients with lesions of peripheral nerves. The circulation was evaluated in some with the usual thermocouple and in others with the plethysmograph. Various measures were used to modify the circulation, mainly application of heat or of cold. The digital vascular reactions accompanying lesions of peripheral nerves were found to be similar to those following sympathetic ganglionectomy. The author expressed the belief that the tendency to coldness of completely denervated digits was due to hypersensitivity to the local vasoconstricting action of the sympathetic fibers. The action of cold was made apparent in denervated digits because of the facilities for loss of heat afforded by vasoconstriction in the remainder of the limb, by the action of epinephrine and by the cooling by disuse. After reactive hyperemia the flow of blood to the denervated

21. Roth, G. M.; Williams, R. D., and Sheard, C.: Skin Temperatures of the Extremities of Persons with Induced Deficiencies of Thiamine, Riboflavin and Other Components of the B Complex, J. Clin. Investigation **23**:373 (May) 1944.

22. Essex, H. E.; Herrick, J. F.; Baldes, E. J., and Mann, F. C.: Observations on the Circulation in the Hind Limbs of a Dog Ten Years Following Left Lumbar Sympathetic Ganglionectomy, Am. J. Physiol. **139**:351 (July) 1943.

23. Richards, R. L.: Vasomotor Disturbances in Hand After Injuries of Peripheral Nerves, Edinburgh M. J. **50**:449 (Aug.) 1943.

24. Doupe, J.: Studies on Denervation: A. Methods, J. Neurol. & Psychiat. **6**:94 (July-Oct.) 1943; B. The Circulation in Denervated Digits, ibid. **6**:97 (July-Oct.) 1943; D. The Mechanism of Axonal Vasodilatation, ibid. **6**:115 (July-Oct.) 1943; E. Observations Concerning Adrenalin, ibid. **6**:121 (July-Oct.) 1943.

digit was commensurate with the needs of the tissues. Doupe concluded by stating the belief that no correlation exists between Raynaud's syndrome and denervation sensitivity, in that the blood flow to the tissues in the presence of lesions of a peripheral nerve is adequate to the needs of the tissue, while with Raynaud's syndrome ischemia occurs. He also expressed the view that the effect of temperature on the vessels is dependent on changes of p_H and resulting changes in metabolism of the tissue. Lowering of the temperature decreases the formation of acid metabolites and so indirectly leads to an elevation of p_H and vasoconstriction. The opposite occurs with heat.

Doupe presented a case report supporting in part the theory of Lewis that the fibers concerned in axonal vasodilatation belong to the posterior root but are not afferent fibers. In his case the ulnar nerve had been sectioned and the median nerve was found to have an unusual distribution. Evidence was presented to show that axonal vasodilatation was mediated in part by fibers other than those associated with sensation. In contrast to the view of Lewis, this author expressed the belief that potent vasodilating substances might be liberated from nerve fibers near their termination.

The same author reported the effects of injections of epinephrine hydrochloride on the circulation of denervated digits and observations indicating the release of natural epinephrine. Like others, he found the vessels of denervated digits with associated degeneration of their sympathetic fibers to have a lowered threshold and a prolonged response to the action of epinephrine, whereas the vessels in preganglionectomized digits showed only a lowered threshold. Conflicting results were obtained concerning the function of epinephrine in regulation of temperature, but the author inferred that the need for conservation of heat did not consistently evoke the secretion of epinephrine. The latter was also true in peripheral neurogenic vasoconstriction. Epinephrine was capable of being liberated in the body in amounts comparable to the intravenous injection of 2.0 micrograms and for longer periods at the rate of 6.0 micrograms per minute. He finally considered that under other circumstances much larger amounts might be liberated and would suffice to initiate a persistent vasoconstriction in a denervated digit.

Potassium.—Rewell [25] reported a significant elevation of serum potassium after the removal of a tourniquet applied to a limb during the course of various orthopaedic procedures. Twelve cases were studied, and the period of ischemia lasted from thirty-five to one hundred minutes. This study lends support to the contention that potassium plays a major role in the production of pain during ischemia. Rewell suggested that the extra potassium in the circulation might come from the ischemic area but that it might also originate in the liver by the action of a hypothetic substance released in the limb.

Anticoagulants.—The popularity of dicoumarin (3,3′-methylenebis-[4-hydroxycoumarin]) and heparin is evident from the increasing number of publications about them. From these a few have been selected for presentation here. A collective review on these preparations was presented by Pfeiffer and Sain.[26]

Attempts are being made to prolong the action of heparin, which would eliminate one of its chief disadvantages. Loewe, Rosenblatt and Lederer [27] administered the drug in the Pitkin menstruum and found this mixture capable of prolonging the coagulation time in rabbits. The effects of a single dose lasted from twenty-four to as much as seventy-two hours. In several animals heparinization was initiated with 50 mg. of heparin in this menstruum and continued as required with 25 mg. doses. In this manner it was possible to maintain adequate heparinization over a two week period with a total dose of 100 mg. This can be contrasted with a two week requirement of 630 mg. of commercial heparin given subcutaneously in fractional daily doses of about 45 mg. The authors expressed the opinion that by further revamping the mixture a more prolonged absorption might occur.

Bryson [28] was also able to prolong the anticoagulant action of heparin by suspending it in a beeswax–sesame oil mixture. For proper suspension the heparin was finely powdered. Studies were performed on dogs. After injections of 100 to 150 mg. of heparin in 0.5 to 1.5 cc. of the beeswax mixture, the coagulation time of the blood was increased for periods which ranged from seventeen to seventy hours. In most instances the coagulation time during these periods was within satisfactory therapeutic limits. Judd, in discussing this method of administration, reported its effect on 5 patients. Two hundred milligrams of heparin in 2 cc. of the 10 per cent mixture of beeswax was injected

25. Rewell, R. E.: Rise in Potassium Concentration in Blood Stream Following Ischemia of Muscle Masses, Brit. M. J. **2**:483 (Oct. 16) 1943.

26. Pfeiffer, D. B., and Sain, F. D.: Heparin and Dicumarol, Internat. Abstr. Surg. **78**:109 (Feb.) 1944.

27. Loewe, L.; Rosenblatt, P., and Lederer, M.: A New Method of Administering Heparin, Proc. Soc. Exper. Biol. & Med. **50**:53 (May) 1942.

28. Bryson, J. C., and Code, C. F.: Prolonged Anticoagulant Action of Heparin in a Beeswax Mixture, Proc. Staff Meet., Mayo Clin. **19**:100 (Feb. 23) 1944.

intramuscularly in most of the patients. The injection was harmless, and an elevation in the clotting time of the blood was produced in each case. The peak of the reaction was reached in twenty-four hours, at which point a "plateau" developed and was maintained for from three to five days. This series is unfortunately too small to permit any definite conclusions.

The synergistic action of heparin and dicoumarin was recently studied by Walker and Rhoads.[29] They reported that under controlled conditions the action of heparin was enhanced by dicoumarin when the prothrombin time was depressed to 20 or 30 per cent of normal by the action of the latter drug. From one half to one third of the usual amount of heparin was needed to produce a given effect in the subjects treated with dicoumarin. This is not unreasonable when one considers that dicoumarin reduces prothrombin and that the susceptibility to the action of heparin is related to the amounts of prothrombin and thrombin in circulation. From a clinical standpoint the importance of this observation is questioned, as the drugs are seldom used together except when quick anticoagulant action is desired, and under these circumstances for a few days only.

Meyer and Spooner[30] found that dicoumarin was absorbed when administered rectally and produced effects similar to those resulting from oral or intravenous exhibition of the drug. There was no change in the latent period by this method of administration. It was inserted either in an aqueous suspension or in a cocoa butter suppository.

McCarter and his colleagues[31] administered various doses of dicoumarin to a series of 29 dogs. The amount administered was far larger than necessary for therapeutic purposes. The animals were killed and the following outstanding morphologic evidences of poisoning were noted: toxic lesions of the small blood vessels sufficient to make hemorrhages almost inevitable, acute renal glomerular swelling and a toxic reaction in the lymphoid tissues. No necrosis of the liver and no consistent hepatic degenerative lesions were found. In 6 dogs receiving dicoumarin at therapeutic levels of dosage, one mild lymphoid tissue reaction was noted.

Autopsies performed on 5 human beings with a variety of diseases who were receiving dicoumarin at the time of death revealed none of the toxic changes just described. In several instances a mild lymphoid reaction could be detected.

Cahan[32] described a patient who received 2,800 mg. of dicoumarin in thirty-two days and had hemorrhagic and purpuric manifestations. There were an associated prolongation of the bleeding time and a pronounced deficiency of prothrombin without reduction in platelets, capillary fragility or abnormality in clot retraction. This patient had received dicoumarin in almost daily doses of 100 mg. during the thirty-two days before he came to the author as a patient. Cahan concluded that toxicity caused by dicoumarin induces not only hypoprothrombinemia but an increased sensitivity of the vascular bed to trauma. This conclusion was derived from the behavior of the skin following a needle puncture tourniquet test.

Lucia and Aggeler[33] recommended vitamin K_1 oxide as a means of treating dicoumarin-induced hemorrhages. He was able to elevate the prothrombin concentration in the blood of a man who had received large doses of dicoumarin by the intravenous injection of 500 mg. of vitamin K_1 oxide. The period elapsing between the institution of treatment with vitamin K_1 oxide and the cessation of the hemorrhagic phenomena was too long to make the method entirely satisfactory.

Morton and co-workers[34] have performed a group of experiments to study the possible influence of vitamin K on thrombus formation in dogs. The radial and saphenous veins of the legs of 52 dogs were traumatized mechanically by scarifying the intima with a hooked needle. The veins were removed at forty-eight and ninety-six hour intervals afterward. Twenty-seven of the animals received a surplus of synthetic vitamin K along with the regular diet for a week prior to the injury, and the remaining 25 were utilized as controls. Determinations of prothrombin and clotting times as well as hematocrit determinations were made at intervals on each animal without demonstrating any effect of the administration of synthetic vitamin K.

29. Walker, J., and Rhoads, J. E.: Effect of Dicumarol on Susceptibility to Action of Heparin, Surgery **15**:859 (May) 1944.

30. Meyer, O. O., and Spooner, M.: The Rectal Administration of Dicumarol, Proc. Soc. Exper. Biol. & Med. **54**:88 (Oct.) 1943.

31. McCarter, J. C.; Bingham, J. B., and Meyer, O. O.: Studies on the Hemorrhagic Agent 3,3'-Methylenebis (4-Hydroxycoumarin): IV. The Pathologic Findings After the Administration of Dicumarol, Am. J. Path. **20**:651 (May) 1944.

32. Cahan, A.: Hemorrhage and Purpura Caused by Dicoumarin, New England J. Med. **228**:820 (June) 1943.

33. Lucia, S. P., and Aggeler, P. M.: Treatment of Dicumarol-Induced Hypoprothrombinemic Hemorrhage with Vitamin K_1 Oxide, Proc. Soc. Exper. Biol. & Med. **56**:36 (May) 1944.

34. Morton, C. B.; Shearburn, E. W., and Burger, R. E.: Synthetic Vitamin K and the Thrombosis of Veins Following Injury, Surgery **14**:915 (Dec.) 1943.

The incidence of thrombosis after injury to the intima of the veins was not significantly increased coincident with the administration of synthetic vitamin K, being 33.0 per cent in the control group and 38.0 per cent in the group given the vitamin K preparation. The small difference was not considered important. The prothrombin values did not significantly change after the administration of synthetic vitamin K. There was no significant difference in the results obtained with synthetic preparations from two different manufacturers. The dogs with a hematocrit reading below 40 per cent, however, revealed a slightly higher incidence of thrombosis in both the control and the vitamin K–fed group.

Clinically, the incidence of thrombophlebitis was less in a small group of women given synthetic vitamin K just before or at the time of delivery than in a larger group receiving no exogenous vitamin K except in the normal diet.

Different results were obtained by Rabinovitch and Pines [35] with heparin. They were able to produce local clot formation in the veins of rabbits by a forcible pull on the vein followed by partial constriction at the site of injury. When heparin was administered even in small doses before injury of the vein and formation of a thrombus, it prevented the subsequent development of a local intravascular clot. The authors also found it unnecessary in their experiments to administer the anticoagulant continuously in order to obtain the desired effects of the drug. In a certain number of animals, heparin proved effective in causing the solution or disappearance of a thrombus, but only when given during the early stages of clot formation. It had no effect when given after the clot had already organized.

Shapiro, Redish and Campbell [36] administered dicoumarin to 18 patients with hepatic disease and hypoprothrombinemia. The dose selected was 50 mg., as this amount was considered one-half the minimal dose capable of prolonging the prothrombin time in normal persons. All of the patients with Laennec's cirrhosis with marked or moderate preexisting prolongation of the diluted plasma prothrombin time showed a definite response to the smaller dose of dicoumarin. Of the 6 patients with slightly prolonged diluted plasma prothrombin time, 3 showed further increase, while those with an initial normal prothrombin time did not respond to dicoumarin. In those in which prolongation did occur the time of the first detectable change was the same as in normal persons.

Wasserman and Stats [37] found that dicoumarin produced a variable response in 71 adult patients. The drug was administered in the usual manner. They expressed the belief that patients receiving this drug must be individualized, as a fixed dosage schedule cannot be made. Of the 8 patients in whom hemorrhages developed, one died. The authors did not elucidate on this patient's case, but it was noted that his prothrombin time was 7 per cent at the time of bleeding. This occurred at the site of an amputation and from the rectum. In 4 other cases transfusions of fresh blood did not arrest the hemorrhagic tendency due to dicoumarin. Several instances were reported in which embolism, thrombosis or progression of existing venous thrombosis occurred despite a low blood prothrombin. The drug failed to produce symptomatic improvement in 10 cases of occlusive peripheral vascular disease during a three month trial. The authors concluded that dicoumarin needs further trial before its effects in cases of peripheral venous thromboses and of pulmonary infarction can be determined.

Evans [38] also emphasized the dangers and disadvantages of dicoumarin, but in his opinion the obvious advantages so far outweigh the dangers of this preventive method if adequate laboratory facilities and proper precautions are observed. Fifty-six patients were treated with dicoumarin alone or with dicoumarin combined with heparin. Of the 4 deaths that occurred, 2 were ascribed directly to dicoumarin poisoning and hemorrhage. Hemorrhagic phenomena were evident in 8 cases (14 per cent). Evans reemphasized the principal precaution in administration of dicoumarin, namely, to determine the morning prothrombin time before ordering the daily maintenance dose. The combined use of heparin and dicoumarin was considered safe only if the doses of heparin were controlled by determinations of the prothrombin time twice daily.

ATHEROSCLEROSIS

The current literature again stresses the importance of the lipids in the causation of atherosclerosis. An excellent review on this subject was recently presented by Hirsch and Wein-

35. Rabinovitch, J., and Pines, B.: Effect of Heparin on Experimentally Produced Venous Thrombosis, Surgery **14**:669 (Nov.) 1943.

36. Shapiro, S.; Redish, M. H., and Campbell, H. A.: Studies on Prothrombin: II. The Effects of a Single Small Dose of Dicumarol (3,3'-Methylenebis [4-Hydroxycoumarin]) in Liver Disease, Am. J. M. Sc. **205**: 808 (June) 1943.

37. Wasserman, L. R., and Stats, D.: Clinical Observations on the Effect of 3,3'-Methylenebis (4-Hydroxycoumarin), Am. J. M. Sc. **206**:466 (Oct.) 1943.

38. Evans, J. A.: Dicumarol Therapy in Thrombotic Emergencies, New England J. Med. **230**:131 (Feb. 3) 1944.

house.[39] The evidence presented in their review favors the opinion that atherosclerosis develops from disturbances in the metabolism of lipids which have infiltrated into the tissues of the intima.

Dauber and Katz [40] reported additional information on the production of atherosclerosis in the chick with cholesterol. By controlled experiments they eliminated the factor of cottonseed oil and simple underfeeding in the production of atheroma. Forty-three 3 month old cockerels were divided into four groups. One group received liberal amounts of an adequate diet for six months. The second group received the same diet plus cottonseed oil. The third group was placed on a regimen of restricted feeding, and the fourth group received the basic mash plus 2 per cent cholesterol in cottonseed oil. Every cholesterol-fed chick acquired atherosclerosis of the thoracic and the abdominal aorta and of their major branches. Atheroma was not present in any of the other groups, but the cockerels not fed cholesterol showed a high incidence of intimal fibrosis of the abdominal aorta with or without lipid. The authors considered the latter pathologic change as an early spontaneous vascular lesion, but in no instance was foam cell atheroma or calcification noted.

Holman [41] confirmed previous work on the experimental production of a necrotizing arteritis in hypertensive dogs with renal insufficiency and also noted that by controlling the diet these lesions were produced with a greater degree of regularity. This was demonstrated by the observation that typical arterial lesions developed in only 5.2 per cent of the hypertensive dogs receiving the regular kennel diet, whereas such pathologic changes developed in 88 per cent of the animals which were fed a specially prepared diet. The latter consisted of calves' liver, cane sugar, corn starch, butter, cod liver oil, a salt mixture, kaolin and tomato juice. It was found necessary to feed this diet prior to the production of renal insufficiency. Certain other factors were found to influence the development of these lesions. Citrate and homologous plasma augmented their production, and a saline-citrate solution not only prevented their occurrence but also protected the dogs against death after a dose of uranium nitrate which had previously proved lethal to 12 of 13 control animals. The author concluded that if a dietary factor was involved in the production of arterial lesions it manifested itself only in the presence of renal insufficiency.

Bruger, Wright and Wiland [42] continued their studies on the effect of testosterone propionate and estradiol dipropionate on the cholesterol content of the blood and of the aorta in female rabbits fed cholesterol. Previous studies had shown that these hormones inhibited the development of hypercholesteremia and prevented disposition of cholesterol in the aorta. The additional studies were done on castrated female rabbits. Testosterone propionate and estradiol dipropionate failed to inhibit the hypercholesteremia and excess deposition of cholesterol in the aortas of the animals that were fed cholesterol, in contrast to its protective action in the normal female rabbit. Control studies revealed that the presence or absence of the female gonad had little influence on the cholesterol content of the blood or of the aorta, normally or after feeding of cholesterol.

An uncommon lesion of smaller arteries was recently described by Sheehan.[43] They were found in organs subjected to roentgen therapy. They consisted of a plaquelike thickening of the intima due to a collection of foam cells alone or of foam cells mixed with various other cells, fluid, fibrin or hyaline material. This was most pronounced between the endothelium and the internal elastic membrane. Occasional changes were noted in the adjacent internal elastic membrane, media and adventitia. These plaques caused a narrowing of the lumen or even occlusion. Thrombosis, fibroblastic proliferation of the intima or deposition of elastic tissue in the thickened intima seldom occurred. The author expressed the opinion that irradiation of the endothelial cells causes not only morphologic changes but also sufficient change in their permeability to permit red cells, as well as lymphocytes and monocytes, to pass through and accumulate in the intima. The disintegration of the red cells or of thrombi in the intima liberates a lipoid substance which is subsequently phagocytosed by monocytes and converted into foam cells. These foam cells closely resemble the early lesions of atherosclerosis.

39. Hirsch, E. F., and Weinhouse, S.: The Role of the Lipids in Atherosclerosis, Physiol. Rev. **23**:185 (July) 1943.

40. Dauber, D. V., and Katz, L. N.: Experimental Atherosclerosis in the Chick, Arch. Path. **36**:473 (Nov.) 1943.

41. Holman, R. L.: Necrotizing Arteritis in Dogs Related to Diet and Renal Insufficiency: V. Evidence for a Dietary Factor, Am. J. Path. **19**:977 (Nov.) 1943.

42. Bruger, M.; Wright, I. S., and Wiland, J.: Experimental Atherosclerosis, Arch. Path. **36**:612 (Dec.) 1943.

43. Sheehan, J. F.: Foam Cell Plaques in the Intima of Irradiated Small Arteries (100 to 500 Microns in External Diameter), Arch. Path. **37**:297 (May) 1944.

EMBOLISM AND THROMBOSIS

Spiegel, Friedlander and Silbert [44] attempted to prevent gangrene in the limbs of cats and dogs by autotransfusion proximal to the site of occlusion. Sufficient ischemia with resulting gangrene was produced by several procedures. Bilateral ischemic paralysis and gangrene of the lower extremities in cats were produced in 10 of 12 experiments in which the three terminal branches of the abdominal aorta and the anastomotic branches of the femoral arteries were ligated. Unilateral ischemic paralysis and gangrene of the lower extremity were produced in cats in 4 of 5 experiments in which the middle hemorrhoidal, the common iliac and the homolateral anastomotic branches of the femoral artery were ligated. In 3 of 6 experiments on dogs, gangrene of the lower extremities was produced by ligating the three terminal branches of the aorta. The authors then transfused the artery proximal to the ligation, and in some experiments pulsations in the vessels returned for several hours. The blood was obtained from donor arteries and in other cases from the abdominal venous reservoir. Even though many failures were encountered and the results none too conclusive, the experiments were of interest and worthy of mention.

Eight additional cases of gangrene of the finger following a digital nerve block were described by O'Neil and Byrne.[45] Although the exact cause for this complication is not known, the authors believed that the injected solution may interfere with the digital circulation and produce gangrene if too much solution is injected, if epinephrine is present in the solution or if tourniquets are used. They also considered the possibility of minimal circulatory damage being aggravated by subsequent soaking of the finger in water sufficiently warm to hasten devitalization of the tissue. They suggested that digital nerve block be replaced whenever possible by general anesthesia. If this is not feasible, small quantities of an epinephrine-free solution should be used without the aid of a tourniquet.

Gangrene as a complication of an infectious disease is uncommon, and only 1 or 2 cases are reported each year. Scarlet fever is the most common offender and children the victims. An interesting series of 3 cases was reported by Kahn and Heubi.[46] The patients were all children from one family who contracted scarlet fever during the same season. All had complicating peripheral thrombosis and 2 of the 3 children subsequently died. Levin and McElroy,[47] also described a case of thrombosis of the right axillary artery following cerebrospinal fever. Gangrene developed and ultimately required amputation.

A case of quadripedal gangrene in a woman of 25 was reported by Fusco and Kell.[48] It was considered to be of syphilitic origin, as no other etiologic factor could be found. Oppenheim and Cohen [49] reported a case of localized gangrene on the hip of a syphilitic patient following an intramuscular injection of mercuric salicylate. They attributed the gangrene to an arterial embolus produced by the crystals of the insoluble mercuric salicylate injected accidentally into a small artery.

Studies on a case of symmetric gangrene of the tips of the extremities due to cold hemagglutination were reported by Stats and Bullowa.[50] The patient was a 64 year old American Negro in whom gangrene developed after moderate exposure to cold. There was no evidence of peripheral vascular disease. Hemoglobinuria was present. No cause could be found to explain the presence of the cold hemagglutinin. There was no evidence of syphilis or hemolytic anemia. The authors were able to demonstrate the presence of localized hemoglobinemia by exposing one limb to cold. Hemagglutination was also produced in the capillaries of the conjunctiva by similar exposure.

THROMBOANGIITIS OBLITERANS

Only a few articles on this disorder came to our attention during the past year. Cases of thromboangiitis obliterans in women were described by Le Fevre and Burns [51] and Atlas.[52]

44. Spiegel, R.; Friedlander, M., and Silbert, S.: Prevention of Gangrene Following Ligation of Major Arteries: Experimental Study, Surg., Gynec. & Obst. **77**:162 (Aug.) 1943.

45. O'Neil, E. E., and Byrne, J. J.: Gangrene of Finger Following Digital Nerve Block: Report of Eight Cases with Discussion of Gangrene Pathogenesis, Am. J. Surg. **64**:80 (April) 1944.

46. Kahn, A. J., and Heubi, J. E.: Postscarlet Fever Thromboses, Quart. Bull. Indiana Univ. M. Center **5**:68 (July) 1943.

47. Levin, A., and McElroy, D. M.: A Case of Cerebrospinal Fever with Thrombosis of the Right Axillary Artery Followed by Gangrene of the Right Arm, Necessitating Amputation, Brit. J. Surg. **31**:240 (Jan.) 1944.

48. Fusco, E. M., and Kell, T.: Luetic Quadripedal Gangrene: Unusual Case, Virginia M. Monthly **70**:611 (Dec.) 1943.

49 Oppenheim, M., and Cohen, D.: Local Arterial Embolism, Arch. Dermat. & Syph. **49**:219 (March) 1944.

50. Stats, D., and Bullowa, J. G. M.: Cold Hemagglutination with Symmetric Gangrene of the Tips of the Extremities, Arch. Int. Med. **72**:506 (Oct.) 1943.

51. Le Fevre, F. A., and Burns, J.: Thromboangiitis Obliterans in Women, Cleveland Clin. Quart. **11**:49 (April) 1944.

52. Atlas, L. N.: Case of Buerger's Disease in Old Woman, Am. Heart J. **26**:120 (July) 1943.

The patient reported on by the latter author was a 68 year old woman, and pathologic studies confirmed his diagnosis. Of additional interest was the fact that she reached the age of 68 before the peripheral vascular disturbance manifested itself clinically.

Edwards and Edwards [53] reported on the pathologic changes in the venous valves in thromboangiitis obliterans. These valves were found to be extensively and seriously damaged. The lesions resembled those found elsewhere in the vascular tree, namely, inflammation, thrombosis and dilatation secondary to the obstruction by these processes. Either the valves were disrupted by the inflammatory process, or their excursion was limited by the extent of involvement on the valve itself or on the adjacent vessel wall. Adhesions were also noted. In obstructive thrombosis the valve was destroyed by the organization and recanalization. In mural thromboses the cusps were incorporated in the organizing tissue or their excursion was limited by thickening and adhesions. The dilatation of the veins distal to areas of obstruction was associated with a relative incompetence of the valve. The growth of the reparative tissue frequently added to the thickness and subsequent rigidity of the cusps.

ARTERIOVENOUS FISTULA

Barber and Madden [54] reported on the spontaneous closure of an arteriovenous fistula in a 24 year old Negro who had been stabbed in the groin. This development tends to support those who advocate a short period of conservative management prior to operation.

PERIARTERITIS NODOSA

During the past year an increasing number of articles were published on this disease. The majority are concerned with the etiology, favoring to a greater extent the theory that periarteritis nodosa is a definite vascular reaction to some allergic mechanism. Case reports are not included in this review; only cases which contribute new information to the problems concerned with this disease are considered.

Rich [55] reported on a series of 5 patients in whom vascular lesions characteristic of periarteritis nodosa followed hypersensitive reactions prior to death. These reactions followed therapeutic injections of foreign serum. Four of these patients had received sulfonamide compounds, but in at least 2 the evidence indicated that the hypersensitive reaction was serum sickness and not drug sensitivity. Similar changes were seen in a biopsy specimen of muscle from a patient who had a hypersensitive reaction following treatment with foreign serum and a sulfonamide compound and in the viscera of a patient who had received prophylactic treatment with sulfathiazole against aspiration pneumonia. None of these patients had any symptoms suggestive of periarteritis nodosa prior to the terminal acute illness for which the serum or sulfonamide compound was administered. The vascular lesions appeared to be fresh. From these observations Rich concluded that the vascular lesions of this type could be a manifestation of an anaphylactic type of hypersensitivity. Continuing his studies in the laboratory, Rich and Gregory [56] established in rabbits a condition analogous to serum sickness in man and produced experimentally typical diffuse periarteritis nodosa. Acute diffuse glomerulonephritis was also noted in a number of animals which had a hypersensitive reaction to the foreign serum. The continued administration of foreign serum or a sulfonamide compound after a hypersensitive reaction had occurred or the injection of a single large amount of foreign serum increased the danger of producing the vascular damage by prolonging the contact of the sensitized body with the offending antigen. The authors suggested as a result of their observations that an attempt should be made to discover and eliminate any inciting antigen in cases of periarteritis nodosa which come under clinical observation.

Harkavy [57] also presented evidence supporting the role of hypersensitivity in periarteritis nodosa. This author has been following 16 cases of bronchial asthma since 1936, 8 of which have been previously recorded. The necropsy observations on 4 of these patients were described. In 2 the basic vascular lesion was similar to periarteritis nodosa. All of the patients showed evidence of a polyvalent sensitivity of bacterial and nonbacterial origin. The simultaneous precipitation of both the asthma and the polymorphous vascular reaction in these cases by the same allergenic stimulation led Harkavy to conclude (1) that bronchial asthma is fundamentally an expression of hyperergic vascular response

53. Edwards, E. A., and Edwards, J. E.: The Venous Valves in Thromboangiitis Obliterans, Arch. Path. **35**:242 (Feb.) 1943.

54. Barber, R. F., and Madden, J. L.: Spontaneous Closure of Arteriovenous Fistula, Arch. Surg. **47**:364 (Oct.) 1943.

55. Rich, A. R.: The Role of Hypersensitivity in Periarteritis Nodosa, Bull. Johns Hopkins Hosp. **71**: 123 (Sept.) 1942.

56. Rich, A. R., and Gregory, J. E.: The Experimental Demonstration that Periarteritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65 (Aug.) 1943.

57. Harkavy, J.: Vascular Allergy: III., J. Allergy **14**:507 (Nov.) 1943.

which may be reversible or irreversible and (2) that the accompanying resultant pathologic changes in the vessels do not represent disease entities but rather are qualitative and quantitative degrees of hyperergic and anergic responses. He believed that these vascular reactions should be attributed to an allergic mechanism.

In contrast to the work of the previous authors, McCall and Pennock [58] presented evidence in favor of the toxic origin of periarteritis nodosa. They drew their conclusions from antemortem studies in 10 cases of this disease. They were unable to correlate the pathologic changes with preceding therapy with sulfonamide compounds. Although all organs were involved, impairment of the renal functioning tissue was the most constant feature of this syndrome. The authors expressed the belief that the arterial lesions pointed either to a disease of the blood vessels caused by a specific bacterial agent or to a specific vascular reaction to some unidentified toxin or other harmful mechanism.

Boyd [59] discussed the cerebral and ocular manifestations of periarteritis nodosa, citing many examples from the available literature. In his opinion the ocular lesions are not distinctive, since the retinal changes cannot be distinguished from hypertension, nephritic syndromes and chronic sepsis. Gaynon and Asbury [60] came to the same conclusion in reporting a case of periarteritis nodosa in which failing vision due to a retinopathy typical of malignant hypertension was the first symptom.

Three interesting cases of polyarteritis nodosa were described by MacKeith.[61] All of the patients presented a localized soft pitting of the skin of one or more limbs together with asymmetric muscular weakness. The diagnosis was made during life and confirmed by biopsy.

Guion and Adams [62] reported the clinical, laboratory and autopsy observations in 6 cases of disseminated lupus erythematosus. Of interest in this review is the observation that although vascular lesions were noted none resembled periarteritis nodosa.

58. McCall, M., and Pennock, J. W.: Disseminated Necrotizing Vascularitis: The Toxic Origin of Periarteritis Nodosa, Am. J. M. Sc. **206**:652 (Nov.) 1943.

59. Boyd, L. J.: The Cerebral and Ocular Manifestations of Periarteritis Nodosa, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **6**:130 (Oct.) 1943.

60. Gaynon, I. C., and Asbury, M. K.: Ocular Findings in a Case of Periarteritis Nodosa, Am. J. Ophth. **26**:1072 (Oct.) 1943.

61. MacKeith, R.: Localized Subcutaneous Oedema with Weakness of Limb Muscles: A Syndrome Due to Polyarteritis Nodosa, Brit. M. J. **1**:139 (Jan. 29) 1944.

62. Guion, C. M., and Adams, E. C.: Six Autopsied Cases of Disseminated Lupus Erythematosus, Am. J. M. Sc. **205**:33 (Jan.) 1943.

TEMPORAL ARTERITIS

The view that temporal arteritis is a local manifestation of a generalized arterial disease gained support by a recent case report of Chasnoff and Vorzimer.[63] In their case the patient appeared to be improving from this disease when she suddenly felt severe pain in the head, vomited, lapsed in a stupor and died. The diagnosis, originally made by biopsy, was confirmed by autopsy. Changes similar to those in the temporal arteries were found in other vessels. A complete pathologic report was withheld pending a future publication.

The findings in the eyes in a previously reported case of temporal arteritis were submitted by Post and Sanders.[64] From their own experience and information obtained from the literature, they concluded that ocular lesions frequently accompany temporal arteritis. These lesions consist mainly of an occlusion of the central retinal artery or other large arteries and a localized arterial lesion with hemorrhages or exudates.

AINHUM

Two additional cases of ainhum were described by Shearer [65] and Ussery.[66] The latter author also presented an excellent review of the literature on this disease. In his opinion it is a disease which is almost exclusively found in dark-skinned races, as it has been observed among white persons in only 4 cases. Heredity does not play a role in its production, and consequently it must not be confused with congenital amputation. It consists in spontaneous amputation of the little toe by an adventitious fibrous band. The author stressed the relationship of the disease to leprosy and to a lesser degree to scleroderma, syphilis, larvae and atavism.

GLOMUS TUMOR

That a glomus tumor may develop at any site was recently emphasized by Cloward and Tilden.[67] They reported a case in which a tumor on the wrist followed local trauma. Love,[68] in reporting a case of subungual glomus tumor,

63. Chasnoff, J., and Vorzimer, J. J.: Temporal Arteritis: A Local Manifestation of a Systemic Disease, Ann. Int. Med. **20**:327 (Feb.) 1944.

64. Post, L. T., and Sanders, T. E.: Temporal Arteritis: Case Report with Eye Findings, Tr. Am. Ophth. Soc. **41**:241, 1943.

65. Shearer, W. S.: Ainhum, Brit. J. Radiol. **17**: 25 (Jan.) 1944.

66. Ussery, G. C.: Ainhum: Review and Case Report, J. M. A. Alabama **13**:319 (April) 1944.

67. Cloward, R. B., and Tilden, I. L.: Glomus Tumor of the Wrist, Hawaii M. J. **2**:299 (July-Aug.) 1943.

68. Love, J. G.: Glomus Tumors, Proc. Staff Meet., Mayo Clin. **19**:113 (March 8) 1944.

described a "pin test" which was of value in localizing the tumor. After the patient's confidence had been gained, the point of a steel pin was pressed into the skin to within 1 cc. of the lesion without producing severe pain, but just as soon as the point was pressed over the lesion excruciating pain developed.

VASOSPASTIC DISORDERS

Immersion Foot.—This condition was described in detail in a previous review. Of the recent articles, only those with additional information are included at this time. An interesting discussion on injuries due to immersion and vasomotor disorders in wartime was noted in the *Proceedings of the Royal Society of Medicine.*[69] Learmonth was the first participant and classified the vasomotor disorders resulting from injury in patients with peripheral vascular disease and those resulting from the local effects of cold. Case histories were described in each group. Ungley and Greene reiterated the subject of immersion foot. Of interest was an abstract by Blackwood, who recorded histologic and experimental observations. The human material which was studied consisted of one foot from a man who died half an hour before rescue and of tissues from extremities of survivors amputated within two to twenty-six months after rescue. In the majority of cases peripheral sepsis was present. The histologic appearance suggested that at the time of immersion damage was done to all the structures in the limb, of a degree and to a level dependent on the length and severity of exposure. Damage to nerves and muscle was striking. The nerves had the greater proportion of their axis-cylinders and myelin sheaths destroyed. Muscular damage appeared to be due to trauma. Hemorrhage from and thrombosis of veins and venules were noted. All of these changes were patchy but became more marked peripherally. Regeneration of the nerves was noted after rescue. Blackwood's original article[70] was recently obtained and found to contain a more detailed description of the pathologic changes in this disorder. His photographs are worthy of commendation.

Experimental studies of immersion foot were also conducted by Blackwood and Russell.[71] They made a histologic study of the changes occurring in the tail of the rat after periods of exposure to cold and wet. The periods and conditions of exposure were comparable to those under which the less severe forms of immersion foot developed in man. This was accomplished by allowing cold artificial sea water to trickle slowly through the bottom of their cages. The depth of water never exceeded ½ inch (1.3 cm.), and the animals were kept in a cold room. The period of exposure varied but seldom exceeded ninety-six hours. On release, some of the animals were allowed to recover slowly; others were warmed up rapidly, and the remaining group were immediately placed in a hot air incubator at 37 C. Conspicuous damage to the muscle and nerve tissue was found to be present after exposures of forty-eight hours. This increased with longer exposures. The skin and other tissues, including blood vessels, appeared much more resistant to chilling. In some of the animals which had been killed two months after exposure the nerve and muscle tissue had not returned to normal, and in others muscle degeneration secondary to denervation was already present. Treatment in the form of the two heating-up processes was found to accelerate the initial reaction, but it made no significant difference in the histologic changes after one month.

It is now well established that in the therapy of immersion foot the extremity must be kept in a cool environment. Ungley[72] was able to accomplish this by exposing the feet of 2 victims to a cool room temperature and having an electric fan play on the soles of the feet. The speed and distance of the fan were adjusted to maintain cutaneous temperatures of 23 to 26 C. (73.4 to 78.8 F.). Cooling to less than 21 C. (69.8 F.) gave rise to discomfort.

Frostbite.—Greene[73] recently reviewed the experimental work on frostbite and reported his results with the albino mouse. This animal was selected because of its convenient size and the standard length of its tail. The mouse was placed in a tube with its tail in a separate compartment which contained solid carbon dioxide at a temperature of — 62 to — 67 C. The degree of frostbite depended entirely on the length of time of exposure. Greene selected one minute and then observed the resultant damage for many days, reporting his observations at various intervals. Early gangrene of the tip was noted at the end of the first day; it had become dry at the eighth day and was self amputating from this time up to the eighteenth day. Studies

69. Discussion on Immersion Injuries and Vasomotor Disorders of Limbs in Wartime, Proc. Roy. Soc. Med. **36**:515 (Aug.) 1943.

70. Blackwood, W.: Studies in the Pathology of Human "Immersion Foot," Brit. J. Surg. **31**:329 (April) 1944.

71. Blackwood, W., and Russell, H.: Immersion Foot, Edinburgh M. J. **50**:385 (July) 1943.

72. Ungley, C. C.: Immersion Foot: Treatment by Dry Cooling, Lancet **1**:681 (May 29) 1943.

73. Greene, R.: Immediate Vascular Changes in True Frostbite, J. Path. & Bact. **55**:259 (July) 1943.

were performed on a smaller group of mice with a longer period of exposure. The studies revealed that in the presence of necrosis the arteries were damaged, with a "silting up" of vessels with cells. In that part of the tail destined to recovery no constant change other than an initial vasoconstriction followed by vasodilatation was observed. This part of the tail had originally been frozen to solidification, as had the adjacent tissue, which became gangrenous. In no case did he find signs of thrombosis in the tails subjected to dry cold. The essential change was a loss of fluid from the blood vessels. Occasionally, damage was so severe that whole blood was lost. Usually only plasma was lost, corpuscles being left stranded within the vessels, which in turn obstructed the blood supply to distal tissues. Thereafter gangrene developed, but only as a secondary change.

That extreme cold is not necessary to produce frostbite was reemphasized by Hamilton.[74] He told of 8 seamen who were employed on the forecastle of a ship in northern waters one early spring afternoon and on the following morning reported with varying degrees of disability as a result of frostbitten fingers. All became wet from an occasional spray coming over the forecastle. As the amount of disability paralleled the duration of exposure without gloves, the author concluded that the wearing of gloves be strictly enforced at all times.

Raynaud's Disease.—The capillary blood pressure of 11 patients with Raynaud's disease and scleroderma was studied by Eichna.[75] Determinations were made before and after sympathectomy. Pressures were measured in the nail folds of the fingers by the direct microinjection method. Measurements were obtained during vasospastic circulatory arrest and also when the blood flow in the capillaries remained visibly unaltered from the normal. During vasospastic circulatory arrest induced in the fingers by cold, the digital capillary blood pressure varied between 7.0 and 12.5 mm. of mercury (average, 9.7 mm. of mercury). The digital capillary blood pressure rose slowly in response to induced increases in venous pressure but fell promptly when this pressure was suddenly lowered. Cessation of blood flow through the capillaries was caused by closure of the proximal vessels. The capillaries, venules and veins remained patent. After a period of vasospastic circulatory arrest, erythrocytes in clumps or loose aggregations could be identified outside the central capillary blood stream on return of the digital circulation. Eichna believed that this was due either to localized constriction of the capillary or to stickiness of the capillary endothelium. In fingers with intact innervation the average digital capillary blood pressure was as follows: arteriolar limb, 18.5 mm. of mercury; summit, 22.4 mm., and venous limb, 19 mm. The gradient of fall of pressure in the capillary was small, usually less than 3 mm. of mercury. In fingers deprived of sympathetic innervation the average digital capillary blood pressure was higher. In the arteriolar limb it was 27.8 mm. of mercury; at the summit, 25.2 mm.; and in the venous limb, 21.6 mm. The somewhat greater capillary pressure in the arterial limb suggests release of arteriolar tone. The gradient of pressure in the capillary remained small (6 to 7 mm. of mercury).

Mufson [76] reported his observations in 6 cases of Raynaud's disease in which a psychosomatic disturbance was present. He expressed the opinion that cooling of the skin was the trigger mechanism which rendered complete the partial occlusion of the minute vessels but that the process was sustained by personality and social-economic derangements. For treating patients with this disease he recommended a combination of measures directed first to an improvement in mental hygiene and alleviation of social-economic derangements and secondly to an increase in collateral circulation. Although this appears to be an ideal type of treatment, it is difficult to accomplish. Three of his patients improved under this regimen, but the others continued to have cyclic vasospasm because they failed to adjust to their environment. Although emotional disorders are known to aggravate Raynaud's phenomena, it is our opinion that the removal of any psychosomatic disorder is beneficial but not curative for the majority of the patients.

Craig [77] also studied the relationship of neuropsychiatric disorders to this syndrome. He measured the digital temperatures of a girl known to have a typical Raynaud syndrome during attacks of panic. This was done under controlled conditions, and when the patient was asked questions intended to create anxiety and tension, a drop in surface temperature was recorded. On one occasion a fall of 9.9 degrees C. (17.8 degrees F.) was noted.

74. Hamilton, J.: Frostbite, J. Roy. Nav. M. Serv. **24**:225 (Oct.) 1943.

75. Eichna, L. W.: Capillary Blood Pressure in Man: Direct Measurements in the Digits of Patients with Raynaud's Disease and Scleroderma Before and After Sympathectomy, Am. Heart J. **25**:812 (June) 1943.

76. Mufson, I.: The Mechanism and Treatment of Raynaud's Disease: A Psychosomatic Disturbance, Ann. Int. Med. **20**:228 (Feb.) 1944.

77. Craig, J. B.: The Psychogenesis of Raynaud's Syndrome, Dis. Nerv. System **5**:142 (May) 1944.

Scleroderma.—During the past few years considerable evidence has been presented to indicate that scleroderma is not necessarily confined to the skin but may involve other organs. Weiss and his colleagues [78] studied a number of cases of generalized scleroderma and reported the clinical histories of 9 cases with signs and symptoms of heart disease. In 2 of these cases postmortem examinations were performed. Cardiac failure was not uncommon, and in the latter 2 cases it was caused by myocardial scarring of an unusual type. These pathologic observations, together with the clinical data, indicated that scleroderma heart disease should be considered a definite entity. In addition to the cardiac findings, the roentgenograms showed involvement of the lungs. Dysphagia was common, and esophageal stricture was noted.

McLaughlin [79] reported a case of diffuse scleroderma following the routine inoculations of a recruit in the armed services. This was confirmed by biopsy and was of further interest because a family history revealed that the patient's father had a similar condition.

Scalenus Anticus Syndrome.—Two variations in this syndrome have recently been observed. Brown [80] reported his observations on a case of scalenus anticus syndrome secondary to a paralysis of the trapezius muscle. It was his opinion that this paralysis had caused sufficient sag of the shoulder girdle to place the scalenus muscle on stretch, with resultant hypertrophy and spasm. The author concluded that other muscular disorders of the shoulder could obscure the diagnosis of this syndrome and consequently it should not be limited to a single diagnostic entity.

Three cases of a vascular disturbance in the upper limb due to compression of the subclavian artery and vein between the clavicle and the thoracic rib were described by Falconer and Weddell.[81] The patients had symptoms similar to the scalenus anticus syndrome. In 1 case cervical ribs were demonstrated and the subclavian artery was found to be compressed at two places, i. e., between the scalenus anterior muscle and the apex of the cervical rib and between the clavicle and the first rib. In a fourth case, in which there were neurologic disturbances only, the subclavian vessels were not compressed, and relief was obtained by section of a fibrous band compressing the eighth cervical and first thoracic nerve roots without division of the scalenus anterior muscle.

The authors were able to demonstrate costoclavicular compression by noting the effect of postural movements of the shoulder girdle on the arterial pulses of the arm. Backward and downward bracing of the shoulders, with or without extension of the head, usually obliterated the pulse. Similar movement was also capable of obliterating the pulse in many normal persons, but in those reported on evidence of compression was demonstrated at operation. Symptoms were noted in only those in whom compression was easily provoked. The symptoms ranged from cold, blue hands with a tendency to chilblains to severe vasospastic attacks, arterial thromboses and even gangrene in the persons with more severe involvement. The authors expressed the belief that persons with mild symptoms will benefit from exercises designed to increase the postural tone in the muscles of the shoulder girdle. For the more severe types operation is required.

Causalgia.—The nature of painful vasodilatation in causalgic states was recently discussed by de Takáts.[82] His conclusions were drawn from a group of 36 cases in which the phenomena of spreading neuralgia and chronic vasodilatation were exhibited. This peculiar vasomotor disturbance has no accepted name, but in de Takáts' opinion it includes Vulpain's *état physiopathique*, Weir Mitchell's causalgia, Sudeck's atrophy, Leriche's post-traumatic painful osteoporosis, the peripheral trophoneurosis and the chronic traumatic edema. Three stages of the syndrome were recognizable after the period of trauma. In the first stage, severe and persistent burning pain, with paroxysmal exacerbations due to jarring, air currents or emotional upsets, was typical. The pain was closely limited to the site of injury. The extremity was warm and dry, and edema was noted. Studies of the blood flow and oscillometric curves indicated increased circulation to the injured parts. The condition might subside or progress to the second stage. The periarticular edema and pain began to spread, and the part was not as warm or as flushed as it was earlier. It often became hard, cyanotic and cold to touch. The blood flow was not as active as in the first stage, but there was

78. Weiss, S.; Stead, E. A., Jr.; Warren, J. V., and Bailey, O. T.: Scleroderma Heart Disease with a Consideration of Certain Other Visceral Manifestations of Scleroderma, Arch. Int. Med. **71**:749 (June) 1943.

79. McLaughlin, R. R. M.: Diffuse Scleroderma, U. S. Nav. M. Bull. **42**:921 (April) 1944.

80. Brown, M. H.: Secondary Scalenus Anticus Syndrome, U. S. Nav. M. Bull. **42**:1164 (May) 1944.

81. Falconer, M. A., and Weddell, G.: Costoclavicular Compression of Subclavian Artery and Vein: Relation to Scalenus Anticus Syndrome, Lancet **2**:539 (Oct. 30) 1943.

82. de Takáts, G.: Nature of Painful Vasodilatation in Causalgic States, Arch. Neurol. & Psychiat. **50**:318 (Sept.) 1943.

a greater tendency to vasodilatation than in the uninjured limb. The pain had the character of a spreading neuralgia or hyperalgesia, which often defied segmental distribution. In the last stage the atrophy progressed, involving skin, muscles and bone, with ankylosis. Atrophy of the bone became diffuse and indistinguishable from osteoporosis of other origin. The pain was intractable. It sometimes spread to the root of a limb or even to the trunk. In this stage section of posterior roots or chordotomy has not been reported to give relief. Ablation of the sensory cortex has been suggested.

The author discussed the phenomena of vasodilatation in the extremities and reviewed the existing evidence for the presence of efferent fibers of the posterior roots. He suggested that cholinergic vasodilator fibers are activated in this condition and that the resulting capillary hypertension is sufficient to account for the pain. Treatment in the early stages consists of immobilization and daily injections of 1 per cent solution of procaine hydrochloride into the injured areas. With a spread of the neuralgia, paravertebral injections are necessary, and for the more severe syndromes a sympathetic ganglionectomy was recommended. The late stage will not yield to such peripheral interruptions and requires intervention by psychiatric, and possibly by surgical, methods.

VENOUS DISORDERS

Mayerson and his colleagues [83] measured venous pressures in 50 unselected patients and found the height of the pressure to be the same in the normal and in varicosed saphenous veins. These measurements were taken with the subjects in the standing position, and in both types of veins the pressures were only slightly higher than the hydrostatic pressure. In the recumbent position, the antecubital and saphenous pressures of patients with varicose veins were found to be significantly higher than normal. This was believed to be due to an increase in blood volume which enabled the subject to compensate for the effects of gravity while standing but led to overcompensation when the recumbent position was assumed.

A new apparatus for the direct measurement of pressure in large and in small veins was described by Burch and Winsor.[84] It is called the phlebomanometer, and from its description it appears to be compact and easy to handle. No comment was made concerning its accuracy. Burch and Winsor [85] also reported their observations on the physiologic effect of ligation of the inferior vena cava in 5 patients. This vessel had been ligated below the level of the renal veins for reasons not disclosed. The venous pressure was markedly increased in the veins of the dorsum of the foot for at least ten months postoperatively. Edema developed immediately after the operation, and in only 1 patient did it subside within the ten month period. The rate of loss of water from the skin of the tip of the right second toe and of the pretibial area was normal at the eighth postoperative day, but no measurements had been taken prior to this time for comparison. The peripheral pulse volumes were decreased. The authors concluded that a satisfactory compensation of the circulation followed this procedure.

Bates [86] reported a case of thrombophlebitis migrans which developed on the twenty-fifth day of scarlet fever. The veins of both legs, including the right external iliac vein, were involved, and improvement followed the use of antiscarlatinal serum.

An interesting case of phlebitis with migratory and disseminate lesions was described by Flood and his colleagues.[87] Gangrene of the mammary gland developed as a unique complication. Striking improvement followed the use of dicoumarin (3, 3′ methylenebis-[4-hydroxycoumarin]). In an "addendum" to the paper, one of the authors mentioned a case of recurrent thrombophlebitis involving a lower extremity in which gangrene of the intestine occurred following a mesenteric thrombophlebitis.

The postmortem observations in a case of thrombophlebitis migrans was recently reported by Swirsky and Cassano.[88] No information was obtained on the cause of the disease. The patient received adequate heparinization, which afforded dramatic and rapid symptomatic relief but failed to prevent further recurrences and thromboses.

83. Mayerson, H. S.; Long, C. H., and Giles, E. J.: Venous Pressures in Patients with Varicose Veins, Surgery **14**:519 (Oct.) 1943.

84. Burch, G. E., and Winsor, T.: Phlebomanometer: New Apparatus for Direct Measurement of Pressure in Large and Small Veins, J. A. M. A. **123**: 91 (Sept. 11) 1943.

85. Burch, G. E., and Winsor, T.: Physiologic Studies on Five Patients Following Ligation of Inferior Vena Cava, Proc. Soc. Exper. Biol. & Med. **53**:135 (June) 1943.

86. Bates, J. V.: Postscarlatinal Thrombophlebitis Migrans, Brit. M. J. **1**:665 (May 29) 1943.

87. Flood, E. P.; Redish, M. H.; Bociek, S. J., and Shapiro, S.: Thrombophlebitis Migrans Disseminata, New York State J. Med. **43**:1121 (June 15) 1943.

88. Swirsky, M. Y., and Cassano, C.: Thrombophlebitis Migrans, J. Lab. & Clin. Med. **28**:1812, 1943.

Rheumatic thrombophlebitis of the left internal jugular vein was discussed by Russek and Abbott.[89] This condition was considered a complication in a patient with inactive rheumatic heart disease. After finding fibrosing Aschoff nodules in the wall of the vessels, the authors concluded that the active rheumatic infection persisted in the vein long after the active infection in the heart had subsided.

In 4 of 40 patients with essential hypertension being treated with potassium thiocyanate, Koffler and Freireich[90] observed a complicating thrombophlebitis. Few supportive data were presented, but the authors said that the frequency of this complication seemed to be greater than could be explained on pure coincidence and that they therefore accepted the drug as the offending agent.

TREATMENT

Nothing new has been added during the past year to the treatment of peripheral vascular diseases. An excellent review of physical medicine in relation to vascular diseases was recently submitted by Allen and Kvale.[91] This includes practically all of the accepted physical agents now used by physicians in this field. The value of this article is greatly enhanced by the frequent comments concerning the personal experiences of the authors.

Warshawsky and Dempsey[92] evaluated the therapeutic response to the three mechanical devices commonly used in treatment of peripheral vascular diseases. These included suction and pressure, intermittent venous occlusion and the oscillating bed. They found the intermittent venous occlusion machine to be the most valuable. Unfortunately, their results were colored by the selection of patients and the frequent use of all three methods. High percentages of improvement were noted with all methods, the least being with the oscillating bed. The authors believed in using all of the methods in a daily routine. The patients were treated from 7 a. m. to 10 p. m. with short rest periods and time for eating. Their schedule included postural exercises, massage with hydrous wool fat or olive oil, whirlpool baths, suction and pressure, sitz baths and intermittent occlusion. Using the combined three methods, they obtained improvement in 82.8 per cent of patients with arteriosclerosis obliterans, 88.9 per cent of patients with arteriosclerosis obliterans and diabetes, 75.9 per cent of patients with thromboangiitis obliterans, 100 per cent of patients with frostbite and 66.7 per cent of persons with residuals of arterial embolism; also in 1 patient with syphilitic endarteritis, 1 with popliteal aneurysm and 2 with arterial thrombosis secondary to polycythemia vera (the only patients with these diseases in the series). No mention was made of the degree of improvement. We do not subscribe to physical therapy in the massive amounts administered, but combinations of a few agents are probably justifiable.

Gambill and Kamenshine[93] described a simple apparatus for administering Buerger's exercises. Unfortunately, the method was not described too clearly. Weights and pulleys helped to elevate and lower the extremities with minimum effort by the patient.

Strong and Wallace[94] administered testosterone propionate to patients suffering from angina pectoris and peripheral vascular disease. The results in angina appeared more promising than those in peripheral vascular disease. Of the 4 patients with the latter disease, 1 reported fairly marked improvement; 2, one of whom was also receiving pavex treatment, said there was slight improvement, and the fourth did not recognize any improvement. Although this series was too small to be of therapeutic significance, its cases can be added to those already published on this questionable method of treatment.

Lakey[95] described a simple apparatus to produce intermittent negative pressure in one or both legs. An ordinary vacuum cleaner was attached to a box to which a clockwork contact breaker had been added to break the circuit every five seconds. The author was able to produce a negative pressure in the box sufficient to raise a column of water 34 cm. He reported his results in 3 cases. Insufficient data cast doubt on the efficacy of this machine, and at best it can be considered only a simple rendition of the more refined pavex boot.

89. Russek, H. I., and Abbott, G. A.: Rheumatic Thrombophlebitis, Am. Heart J. **26**:542 (Oct.) 1943.

90. Koffler, A., and Freireich, A. W.: Thrombophlebitis, Am. J. M. Sc. **207**:374 (March) 1944.

91. Allen, E. V., and Kvale, W. F.: Physical Medicine in Vascular Diseases, M. Clin. North America **27**:951 (July) 1943.

92. Warshawsky, H., and Dempsey, M. W.: Physical Therapy of Peripheral Vascular Disease, Arch. Phys. Therapy **24**:487 (Aug.) 1943.

93. Gambill, I. M., and Kamenshine, A.: Apparatus for Buerger's Exercises, M. Bull. Vet. Admin. **20**:173 (Oct.) 1943.

94. Strong, G. F., and Wallace, A. W.: Treatment of Angina Pectoris and Peripheral Vascular Disease with Sex Hormones, Canad. M. A. J. **50**:30 (Jan.) 1944.

95. Lakey, E. O.: Pulsator Vacuum Box for Treatment of Peripheral Vascular Disease, Lancet **2**:767 (Dec. 18) 1943.

(To Be Continued)

Book Reviews

Health and Hygiene: A Comprehensive Study of Disease Prevention and Health Promotion. By Lloyd Ackerman. Price, $5.00. Pp. 895. Lancaster, Pa.; The Jacques Cattell Press, 1943.

This book is one of the best for the layman. The author, urged on by the belief that no field of study and instruction has greater potentialities for promotion of the welfare of the individual and society than hygiene has, has emphasized those aspects which concern the average normal person and which he can to some extent influence. Ackerman feels that instruction in hygiene in college is best given during the last two years of the regular course or during the first years of professional education, when the student is best prepared to realize its greatest benefits. The text is therefore meant for a more mature reader than most such works.

The book starts with a discussion of the hygienic concept and reveals the nature, magnitude and objectives of hygiene. This section is followed by a survey of the mortality and morbidity experience of the United States in recent years and a discussion of the prevalence of physical defects and mental disorders. These discussions are well developed and should be easily understood by an adult layman. The evolution of concepts of health is developed from the historical standpoint, leading to the modern experimental approach and methods of evaluation. The reader is then introduced to parasitism and hypersensitiveness, hygiene of the mouth, nutrition, emotions and the intellect, mating and finally exogenous poisons, physical agents and their relations to disease. It is noteworthy that of the 863 pages of text 167 are given to hygiene of the emotions and the intellect and 95 to the hygiene of mating.

The subject is covered in a comprehensive, readable fashion which gives the reader a good grasp of the entire subject.

A Visit to Le Puy-en-Velay. By Harvey Cushing, M.D. Price, $8.00. Pp. xiv + 40, with 31 illustrations. Cleveland: The Rowfant Club, 1944.

This recent publication of the Rowfant Club presents a side of Dr. Cushing which all who knew him will appreciate. The volume is a small one, beautifully printed, made from a diary that he kept in 1900, when he was 31 years old and when he traveled abroad by way of a vacation after he had completed his surgical residency at the Johns Hopkins Hospital.

The diary makes pleasant reading. Even more attractive are the illustrations—mainly sketches with a few water colors—which he drew or painted, perhaps to make his diary more vivid or perhaps for his own entertainment.

Too often, the inconsequential—many times the most charming—characteristics of leaders are lost because they are expressed so inadequately in biographies. This bit of Cushing, composed by himself, gives an intimate glimpse of his companionableness, his artistry, his alertness in observation, his humor and his ability to express himself originally in any medium at hand. The Rowfant Club deserves hearty congratulations for making this unique contribution to medical history.

American Medical Practice in the Perspectives of a Century. By Bernhard J. Stern. Price, $1.50. Pp. 156. New York: The Commonwealth Fund, 1945.

The New York Academy of Medicine and the Commonwealth Fund, either alone or in combination, are likely to do things well. This book is worthy of both sponsors.

The monograph is well written and gives an amiable account of recent medical history as it has influenced or has been influenced by economic changes, industry, education, urbanization and American life in general. The conclusion is sound: The chief problem of medical practice that agitates the public today is providing for every one a high quality of curative and preventive medical service.

The author, a doctor of philosophy and sociologist, says that the future prestige of the medical profession and the future contribution of medicine to scientific and social progress are closely related to the solution of this problem. He does not give the answer.

Medical Uses of Soap. Edited by Dr. Morris Fishbein. Price, $3.00. Pp. 182, with 41 illustrations. Philadelphia: J. B. Lippincott Company, 1945.

The statement on the jacket of this book, "Many scattered articles have appeared on specific medical uses of soap, but never before has a reference written by leading authorities so adequately covered this field," summarizes the contents and purpose. Chemistry, process of manufacture, effects on skin and hair, soaps suitable for industrial workers, soaps for shaving and the medical uses of soap are all discussed by experts. The book should be valuable to dermatologists, industrial physicians and others.

An Outline of Tropical Medicine. By Otto Saphir. Pp. 86. Chicago: The Michael Reese Research Foundation, 1944.

Several books of varying size and importance have been published recently, all dealing with tropical medicine. The author of this one terms it neither a textbook nor a handbook but rather an extended vocabulary of the language with which those who practice medicine in the tropics must be familiar.

He writes clearly and has managed to compress a large stock of information within a few pages. The book fits into one's pocket nicely. It will be useful to many readers. It deserves a cordial reception.

El síndrome de Morgagni. By Carlos A. Campos. Pp. 150, with 12 illustrations. Buenos Aires, Argentina: Iglesias y Matera, 1943.

Dr. Campos presents a complete discussion of Morgagni's syndrome in this work. The syndrome is described as occurring most frequently in women between the third and sixth decades of life. Cardinal symptoms are a symmetric hyperostosis of the internal table of the frontal bone with a varying neurologic or neuropsychiatric picture. Concomitant obesity is present in about one half of the cases.

The history of the syndrome is reviewed, and a report on 12 cases is included. All of the patients described were women between 30 and 80 years of age; the majority were in the menopause. Eight had arterial hypertension, and 11 had obesity of the rhizomelic type. All had endocranial hyperostosis, localized in the ascending or vertical part of the frontal bone. This symptom, Dr. Campos believes, is fundamental and must be present for diagnosis. He classifies hyperostosis into: (1) internal frontal hyperostosis, the most common and characteristic type; (2) nebula frontalis; (3) diffuse hyperostosis of the calvaria, and (4) frontoparietal hyperostosis.

A complete clinical study of the syndrome is presented, and Dr. Campos believes future studies and theories must keep the following points in mind: (1) Morgagni's syndrome is characterized by a familial tendency; (2) it is almost completely limited to women, the ratio of women to men being 22 to 1; (3) there is pleomorphism between this syndrome and constitutional obesity; (4) the syndrome is vinculated to acromegaly and other pictures of anterior hypophysial hyperfunction; (5) it indicates disposition to nervous and mental diseases. Dr. Campos encourages physicians to consider Morgagni's syndrome a "heredopathologic syndrome."

The book fulfils its purpose, the presentation of Morgagni's syndrome. Because of the rarity of the disorder, the work is of limited value to the average internist, but it may be of considerable service to those who have a special interest in this type of disease.

Atlas of the Blood in Children. By Kenneth D. Blackfan and Louis K. Diamond. Price, $12.00. Pp. 320, with 70 plates. New York: The Commonwealth Fund, 1944.

By tradition the word atlas signifies a book of maps. This particular one is an excellent book of maps revealing how that territory which includes diseases of the blood in children can best be explored.

The contents are arranged ingeniously: About half is devoted to a short monograph describing how blood cells originate, how they look and what happens to them when they become abnormal, and about half is comprised of excellent colored illustrations. The text is not entirely orthodox, for the authors are teachers and have enlivened their style by using words which are known to be popular with students. The various kinds of blood dyscrasias not only are described readably but are illustrated with good diagrams and case records.

The colored plates are works of fine artistry. Each plate has an accompanying diagram, so that any reader can easily find on the plate exactly what he is intended to see. There are enough plates to illustrate almost every type of blood smear.

Diseases of the blood in children are so comparable to diseases of the blood in adults as to make the volume useful to any clinician. The book deserves high praise. Students, practicing physicians and clinical laboratory workers will wish to have it at hand. A copy of it should be found in every hospital and medical school library.

Textbook of Medical Treatment. By various authors. Price, $8.00. Pp. 1218, with 26 figures and 4 tables. Baltimore: Williams & Wilkins Company, 1944.

This book is an excellent conservative statement of modern treatment in internal medicine. It is interesting to compare British and American practice and to find almost complete correspondence, certainly as to fundamentals. Two minor criticisms may be made: First, some prescriptions are given in metric units and others in apothecaries' units; second, some space is perhaps used to little advantage in brief discussions of treatment of rare or relatively unimportant conditions.

News and Comment

Hermann M. Biggs Memorial Lecture. — The Hermann M. Biggs Memorial Lecture will be delivered by F. C. Bishopp, Ph.D., assistant chief in charge of research, Bureau of Entomology and Plant Quarantine, United States Department of Agriculture, in Hosack Hall, New York Academy of Medicine, on Thursday, April 5, at 8:30 p. m. The subject will be "The Medical and Public Health Importance of the Insecticide DDT." The lecture will be given under the auspices of the Committee on Public Health Relations and will be open to the public.

New York Institute of Clinical Oral Pathology. —The New York Institute of Clinical Oral Pathology will hold its one hundredth monthly conference at the New York Academy of Medicine on Monday evening, April 30. The subject of the meeting will be "A Survey of the Antibiotic Problem." This will be discussed by members of the medical and dental professions both from the theoretic and from the clinical standpoint. Members of the medical, dental, public health and other professional groups are cordially invited. For further information communications should be addressed to the executive secretary, 101 East Seventy-Ninth Street, New York 21.